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Bridging the gap in asthma management among adolescents and young adults

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Bridging the gap in asthma management among adolescents and young adults

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Abstract

Background: Asthma can develop at any age. During childhood, the prevalence of asthma is higher in boys, but after puberty it grows higher in girls. The goals of asthma treatment are to achieve and maintain asthma control and to reduce future risks of exacerbations. Most children with asthma have a mild or moderate disease. However, a small proportion have severe asthma. Patients with severe asthma have the largest disease burden and require more healthcare resources than those with mild-to-moderate asthma. In adolescence, asthma management involves a transition from pediatric to adult healthcare, meaning that changes in care and pharmacological treatment may occur.

Aim: The overall research aim of this thesis was to characterize asthma in adolescence and young adulthood, with a particular focus on sex and severity, and to identify factors of importance for improved asthma management during the transition from pediatric to adult healthcare.

Methods: All four studies in this thesis were based on the ongoing Swedish population-based birth cohort BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology). This birth cohort includes 4,089 participants, followed from infancy up to age 24 years. Information about symptoms and treatment related to asthma and other allergic diseases were assessed through repeated questionnaires. At ages 4, 8, 16 and 24 years, the participants were also invited to undergo a clinical examination including for example blood sampling and measurements of lung function, height, and weight. To address the specific aims in this thesis, BAMSE data were linked to data from national and regional registers for asthma-related healthcare consumption and dispensed medications. In addition, qualitative data were obtained through individual interviews.

Results: In **Study I**, 14% fulfilled the study definition of asthma at 16 years of age (15% among females vs. 13% among males, $p = 0.22$). Almost half had uncontrolled asthma (46%). In total, 24% ($n = 104$) of the adolescents with asthma were dispensed high daily doses of inhaled corticosteroids (ICS) or fixed combinations of ICS and long-acting β_2-agonists within the preceding 18 months. This was more common among males than females (29% vs. 19%, $p = 0.02$). Moreover, 7% ($n = 24$) had severe asthma (6% of females vs. 7% of males, $p = 0.61$).

In **Study II**, four categories emerged based on the young adults' experiences of their asthma healthcare: "I have to take responsibility," "A need of being involved," "Feeling left out of the system," and "Lack of engagement." The young adults felt they were given more responsibility, did not know where to turn, and had fewer follow-ups in adult healthcare. Further, the participants wanted healthcare providers to involve them in self-management

already during adolescence, and felt that their asthma received insufficient attention from healthcare providers.

In **Study III**, 8% (n = 147) had persistent asthma. Among those with persistent asthma, register data showed that 39% (58 of 147) had at least 1 healthcare consultation within the 4-year period preceding their 18th birthday and 37% (55 of 147) in the 4-year period following that date. The mean number of healthcare consultations in the 4-year period preceding age 18 years was 1.6, compared with 1.0 in the 4-year period after age 18 years ($p = 0.02$). At least 1 dispensation of any ICS before age 18 years was found for 73% (107 of 147), compared with 50% (74 of 147) after age 18 years. On average, the participants with persistent asthma were dispensed ICS 3.1 times in the 4-year period preceding age 18 years and 2.1 times in the 4-year period after age 18 years ($p < 0.01$). Only 3% of the persistent subjects (5 of 147) had a regular dispensation of any ICS once a year during the 8-year period.

In **Study IV**, a latent class analysis was performed, and a 4-class solution of asthma trajectories was identified: never/infrequent (n = 3,291, 80%), early-onset transient (n = 307, 8%), adolescent-onset (n = 261, 6%), and persistent asthma (n = 230, 6%). Uncontrolled asthma was equally prevalent in the adolescent-onset and persistent asthma trajectory groups, at both 16 (42% vs. 42%, $p = 0.90$) and 24 years of age (54% vs. 52%, $p = 0.81$). The persistent asthma trajectory group had a higher proportion of eosinophil counts ≥ 0.3 (10^9 cells/L) at 24 years of age compared with the adolescent-onset trajectory group (31% vs. 19%, $p < 0.01$).

Conclusion: Based on the results from this thesis, it could be concluded that asthma was common in adolescence and young adulthood, and a shift from male to female dominance occurred during adolescence. Further, many adolescents and young adults had few asthma-related healthcare consultations and dispensed asthma medications. Moreover, the adolescents and young adults with more recent onset of disease had equal burdens of respiratory markers as those who had persistent symptoms.

List of scientific papers

This thesis is based on the following four papers, which are referred to in the text with Roman numerals.

I. **Ödling M**, Andersson N, Ekström S, Melén E, Bergström A, Kull I. Characterization of asthma in the adolescent population. *Allergy*. 2018;73(8):1744-6.

II. **Ödling M**, Jonsson M, Janson C, Melén E, Bergström A, Kull I. Lost in the transition from pediatric to adult healthcare? Experiences of young adults with severe asthma. *The Journal of Asthma: Official Journal of the Association for the Care of Asthma*. 2020;57(10):1119-27.

III. **Ödling M**, Andersson N, Hallberg J, Almqvist C, Janson C, Bergström A, Melén E, Kull I. A gap between asthma guidelines and management for adolescents and young adults. *The Journal of Allergy and Clinical Immunology: In Practice*. 2020;8(9):3056-65 e2.

IV. **Ödling M**, Wang G, Andersson N, Hallberg J, Janson C, Bergström A, Melén E, Kull I. Characterization of asthma trajectories from infancy to young adulthood. *The Journal of Allergy and Clinical Immunology: In Practice*. 2021 (in press).

Contents

List of abbreviations

95% CI:	Ninety-five percent confidence interval
ACT:	Asthma control test
ANOVA	One-way analysis of variance
ATC:	Anatomical therapeutic chemical
BAMSE:	Barn/child, allergy, milieu, Stockholm, epidemiology
BIC:	Bayesian information criterion
BMI:	Body mass index
COPD:	Chronic obstructive pulmonary disease
CRC:	Clinical Research Collaboration
EAACI:	European Academy of Allergy and Clinical Immunology
ERS/ATS:	European Respiratory Society and American Thoracic Society
FeNO:	Fractional exhaled nitric oxide
FEV_1:	Forced expiratory volume in 1 second
FVC:	Forced vital capacity
GINA:	Global initiative for asthma
GLI:	Global lung function initiative
GRADE:	Grading of recommendations, assessment, development, and evaluation approach
HRQoL:	Health-related quality of life
ICD-10:	International statistical classification of diseases, version 10
ICS:	Inhaled corticosteroids
IgE:	Immunoglobulin E
ISAAC:	International study of asthma and allergies in childhood
kU_A/L:	Kilounits per liter
LABA:	Long-acting β2-agonists
LCA:	Latent class analysis
LLN:	Lower limit of normal
LTRA:	Leukotriene receptor antagonists
MAS	German Multicentre Allergy Study
MEFV:	Maximal expiratory flow volume
MeDALL:	Mechanisms of the development of allergy
OR:	Odds ratio

PIAMA:	Prevention and incidence of asthma and mite allergy
PPB:	Parts per billion
SABA:	Short-acting β_2-agonists
SHARP:	Severe Heterogeneous Asthma Research collaboration, Patient-centered
SPDR:	Swedish Prescribed Drug Register
STC:	Systematic text condensation
VAL:	Stockholm Regional Healthcare Data Warehouse
WHO:	World Health Organization

1 Background

1.1 Asthma

Asthma is a chronic respiratory disease, categorized by variable symptoms of wheeze, chest tightness and/or cough, shortness of breath, and expiratory airflow limitation (1). Symptoms and airflow limitation vary over time and in intensity, and can be triggered by a number of factors, such as allergen or irritant exposure, exercise, weather change, or viral respiratory infections (1-5). Asthma is a heterogeneous disease with several different underlying disease processes, and clinical manifestations that typically vary with age.

Figure 1 shows an overview of asthma as interpreted in this thesis regarding development, diagnosis, and management.

Figure 1. An illustration of asthma and risk factors (environment, socioeconomic status, and heredity) for development of the disease, as well as the diagnosing and management of asthma.
Illustrated for this thesis by FB Scientific Art Design 2021.

1.1.1 Disease development and epidemiology

Asthma is known to be a heritable disease (6, 7), with the heritability of childhood asthma estimated at around 80% (7). Family history of asthma is a risk factor, and the associations have been found to be more pronounced for maternal than paternal asthma (8, 9). In addition, exposures already in utero are of importance (10). Complex diseases like asthma appear to be caused by a combination of genes and the environment (10). Established environmental factors are, e.g., second-hand tobacco smoke exposure and air pollution (1, 11). Socioeconomic status has been associated with risk of asthma in many studies, and reflect lifestyle differences in, e.g., diet, infections, and access to healthcare. Other possible risk factors for development of asthma have been suggested. For example, breastfeeding for 4 months or more seems to reduce the risk of asthma in early childhood (12). Asthma continues to develop throughout childhood, and childhood overweight and obesity have been associated with the disease (13). Although having siblings at home is associated with wheezing episodes in early life, it is likewise associated with protection against the development of childhood asthma (5). Further, considerable controversy exists regarding pet ownership, and particularly if cat and dog exposure may be a risk factor or a protective factor for developing asthma (14).

The so-called atopic march constitutes the progressive development of allergic diseases, where allergic diseases begin in early life with eczema, progress through food allergy, and culminate in rhinitis and asthma later in childhood (15-18). Moreover, asthma, eczema, and rhinitis often co-occur, and are commonly classified as allergic co-morbidities (19). Allergic diseases have in common that genetic and environmental factors are interlinked through both immunoglobulin E (IgE)-associated and non-IgE-associated mechanisms (20). About half of individuals with asthma have underlying IgE-associated mechanisms, and the other half have non-IgE-associated mechanisms. IgE-associated mechanisms are characterized by a hyperreactivity of the immune system to usually harmless allergens in the environment. Individuals who have IgE antibodies with a specificity for a certain allergen are said to have allergic sensitization – they are sensitized (21).

The international differences in asthma symptom prevalence among children have decreased over the last decades; symptom prevalence has decreased in Western Europe, while it has increased in regions where it was previously low (1). In Eastern Europe, Asia, Latin America, and Africa, asthma symptoms continue to grow more common. The global prevalence of current wheeze based on a written questionnaire ("Have you had wheezing or whistling in your chest in the past 12 months?") in 2000–2003 (no new worldwide data since 2003) among 13–14-year-old children was 14.1% (22). **Figure 2** is a world map showing the prevalence of asthma in adults by country, which appears to vary between 1 and 22%

worldwide (1). However, reliable comparisons of reported prevalence rates in the world may be difficult to make due to a lack of universally accepted definitions of asthma.

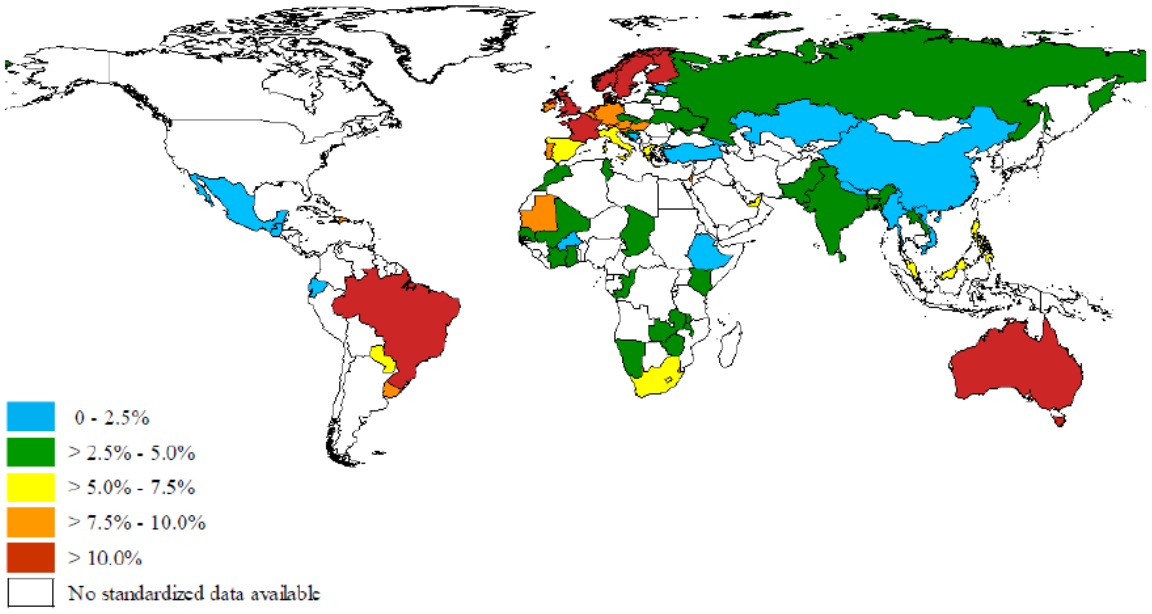

Figure 2. World map of the prevalence of asthma in adults by country. Data based on doctor-diagnosed asthma and/or ever treated for asthma and/or taking asthma medication in the preceding 2 weeks.

In early childhood, prevalence of asthma is highest among boys, but after puberty, asthma becomes more common among females (23-26). The reasons for this are not clear, but one contributing factor is differences in lung and airway size; in infancy, lungs and airways are smaller in boys than girls (1). Other explanations for this sex shift include hormonal changes and sex-specific differences in environmental exposures, e.g., smoking (23). Another explanation involves the underdiagnosing and undertreatment in females compared with males.

Predicting who will remit and who will have persistent asthma is difficult, as certain forms might persist from infancy into adulthood, while others are associated with high likelihood of remission (2, 3). Results from epidemiological studies show that family history of asthma and atopy, co-morbidity, lung function deficits, and infections in early life are associated with persistent asthma symptoms (2, 27-30). Further, mild asthma often goes into remission, whereas severe asthma is more likely to persist (2, 31).

Rationale for **Study I**

The prevalence of childhood asthma differs between populations and the observed prevalence may depend on the applied study design and definition (32). Therefore, in **Study I,** which was the starting point of this thesis, the focus was on asthma in the adolescence period using a definition of asthma based on the large European MeDALL (Mechanisms of the Development of ALLergy) project (33). Further, the research group characterized asthma with respect to sex and clinical characteristics, using a birth cohort from the general population.

1.1.2 Diagnosis and definition

In clinical practice, asthma in children is typically diagnosed based on the history of respiratory symptoms, such as wheeze, chest tightness, shortness of breath, and cough, together with variable expiratory airflow limitation (1). There are also several standardized techniques used to diagnose and monitor airway disease (such as asthma), with the choice of technique determined by the aim of the examination and the age and ability of the patient. Dynamic spirometry is the most commonly used method for measuring lung function in clinical practice and research, in both children and adults (34). It has yet to be confirmed if fractional exhaled nitric oxide (FeNO) is useful in the diagnosis of asthma (1). However, biomarkers such as FeNO and blood eosinophils may be used as markers of eosinophilic airway inflammation (1, 35). FeNO and blood eosinophils (and lung function measurements) have been investigated and are further described in this thesis.

In epidemiological studies, asthma is often defined based on a combination of symptoms, doctor's diagnosis and medication use – reported by parents in studies of young children or by the participant him- or herself in studies of adolescents and adults (36).

1.1.3 Phenotypes and trajectories

One way of characterizing asthma is to divide it into phenotype, endotype, and trajectory (37). Broadly, a phenotype can be described as a specific clinical characteristic. Several phenotypes have been identified, with respect to, e.g., age at onset of asthma (childhood vs. adulthood), clinical factors (episodic vs. persistent), inflammatory factors (eosinophilic vs. non-eosinophilic), immunological factors (atopic vs. non-atopic), and severity (treatment needed to achieve control) (1, 5). Endotype refers to the underlying biological mechanism and pathogenesis, for example allergic asthma, where asthma can be associated with IgE

sensitization (37). A trajectory refers to the longitudinal perspective of a trait (e.g., lung function), a symptom (e.g., wheeze), or a phenotype (e.g., a certain asthma type).

Previous research studying the natural history of wheezing in childhood was initially based on a hypothesis-based approach (38), later supplemented by hypothesis-free data-driven approaches, such as latent class analysis (LCA) (39). A recent meta-analysis included thirteen cohorts from the general and at-risk populations and used latent trajectory methodology to identify wheeze trajectories and associated risk factors (40). Five trajectories were identified, but the follow-ups varied in length between 3 and 18 years, with a mean length of about 10 years, and the authors concluded that more studies with consistent factor definitions and longer follow-ups were needed to improve evidence on childhood wheeze trajectory-specific factors.

Rationale for **Study IV**

More research was needed to confirm asthma trajectory groups defined by age at onset, and to improve evidence on asthma trajectory-specific factors up to young adulthood. This was in part due to that the number of trajectories identified, and their specific patterns, varied somewhat between different populations and lengths of follow-up (41). Unlike most prior studies (40, 42-47), **Study IV** provided the possibility to cover a period from infancy up to 24 years of age. By investigating trajectories using an unbiased LCA, the research group aimed to provide increased knowledge about asthma development that might be translated into better treatment approaches, personalized medicine efforts, and – ultimately – improved disease outcomes (4, 48).

1.1.4 Management

Management of asthma is based on various asthma guidelines or recommendations, with GINA being one (1). GINA is based on the best evidence and medical knowledge and practice at the time of publication (1). Further, the European Respiratory Society and the American Thoracic Society (ERS/ATS) make recommendations for patient care that are informed by systematic reviews or pragmatic evidence syntheses formulated and graded using the Grading of Recommendations, Assessment, Development, and Evaluation approach (GRADE). In this thesis, GINA and ERS/ATS are the primary references; there are also national guidelines developed by, e.g., the Swedish Paediatric Society (49) and the Swedish National Board of Health and Welfare (50), and local guidelines used in clinical practice.

In the delivery of asthma management, there is variation between healthcare systems, with specialists delivering treatment in some countries, and primary healthcare providers doing so in others (1). There is also variation in the quality of asthma management, services across asthma specialists and primary care clinicians, and adherence to guidelines (51-54).

1.1.4.1 Pharmacological treatment

Pharmacological treatment is a cornerstone in all asthma guidelines and the basic long-term asthma treatment includes the following medication classes: short-acting β_2-agonists (SABA; reliever medication) and long-acting β_2-agonists (LABA; to be used together with a controller medication), and the controller medications inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA) (36, 55). For moderate to severe asthma, other types of controller medications are also available. Reliever medications are used as-needed for relief of breakthrough symptoms (1). Controller medications are used to reduce airway inflammation, risk of exacerbations, and control symptoms and lung function decline. GINA recommend that all adolescents and adults should receive as-needed low dose ICS/formoterol to reduce their risk of serious exacerbations and to control symptoms, and no longer recommend treating with SABA alone (56).

However, a recent study showed that only 20% of adults used their inhaler correctly and in a timely fashion (57). In general, adherence to asthma medications is low in all age groups (58, 59). Adherence is defined by the World Health Organization (WHO) as follows: "the extent to which a person's behavior corresponds with agreed recommendations from healthcare provider" (60). Adherence to medications can further be divided into three steps: initiation (taking the first dose), implementation (how a patient's actual dosage corresponds to the prescribed dosage), and persistence (time from initiation until interruption of treatment) (61-63).

The long-term goal of asthma treatment is to achieve and maintain asthma control, reduce future risks of asthma exacerbations, and enable living without restrictions (1, 8, 64). It is therefore important to regularly monitor symptoms and response to treatment at an appropriate level of care. The level of asthma control is the extent to which the manifestations of asthma can be observed in a patient, or have been reduced or removed by treatment (1). An example of assessing asthma control in clinical practice is using the validated Asthma Control Test (ACT), which encompasses four questions on symptoms/relievers and one question on self-assessed level of control (65). Most asthma patients can achieve symptom control and minimal exacerbations with regular controller treatment, but some will not, even with maximal therapy (1, 55). In some patients, this is due to severe asthma, but in others it is due

to, e.g., comorbidities or persistent environmental exposures (1). A smaller proportion of patients with asthma have severe asthma (66-69). The prevalence of severe asthma is difficult to assess because different definitions are used, but has been estimated to be around 5–10% of the entire asthma population (70-72). The ERS/ATS and GINA guidelines are often used for classification of severe asthma (1, 73). Severe asthma is characterized by frequent and severe manifestations which do not respond to treatment or only respond to high doses of anti-inflammatory and other controller medications (69). Before the diagnosis of severe asthma, patients need to go through a systematic assessment (35, 74), in order to differentiate between "difficult-to-treat" (where poor control is related to, e.g., poor adherence or co-morbidities), and "true severe asthma."

Further *rationale* for **Study I**

Most studies to the date of planning for **Study I** described severity of asthma throughout childhood (75-79), without studying the adolescence period separately. In a healthcare setting, it is important to identify patients with severe and uncontrolled asthma to gain insight into how pharmacological treatment can be tailored and to understand how risk factors can be modified (80-82). Further, to capture the relevant phenotypes of children with severe asthma, a careful and broad clinical characterization is required (66).

1.1.4.2 The transition from pediatric to adult healthcare

In early childhood, management is dependent on caregivers, who have the responsibility of evaluating asthma symptoms, following treatment plans, and obtaining medication (83). School-aged children begin to gain some level of autonomy, but rely on adults for assistance. For adolescents, attaining self-management is one goal. Adolescence is a challenging phase in life, particularly when compounded with a chronic disease (73, 84, 85). Critical objectives during adolescence are to acquire the confidence, knowledge, and skills that are required to be an independent, expert adult patient (86). This process is known as a transition, here with a focus on the developmental transition. There are four types of transitions, and adolescents with a chronic disease experience three of these – developmental (moving from adolescence into adulthood), health/illness (going from pediatric to adult healthcare), and organizational (changes in leadership, changes in care environment) (87). The fourth type is "situational," e.g., beginning a new job or changing jobs. In this thesis, the focus is on the transition from pediatric to adult healthcare, and the terms "transition" and "transfer" are used interchangeably, as they often are in the literature (**Figure 3**). In Sweden, most children with severe asthma and/or asthma in combination with multiple allergic diseases are treated at

specialized pediatric community clinics or allergy clinics at children's hospitals (49). At around patient age 18 years, asthma management includes a transition from pediatric to adult healthcare (88). There are many definitions of this transition, such as "a purposeful, planned process that addresses the medical, psychosocial, and educational/vocational needs of adolescents and young adults with chronic physical and medical conditions as they move from child-centred to adult-oriented healthcare systems" (85, 89-91).

Figure 3. An illustration of the transition from pediatric to adult healthcare.
Illustrated for this thesis by FB Scientific Art Design 2021.

In pediatrics, a patient often goes to the same physician at a specialized pediatric community clinics for many years, in contrast to in adult healthcare, where a patient often visit multiple clinics and see different physicians to meet all of their needs, which could be a barrier to successful transition (92). In other words, for individuals with a chronic disease like asthma, the transition period can be challenging (93). However, successful support during this period could provide patients with lifelong skills related to how to manage their asthma and thereby reduce the impact of the disease (86). The transition should, according to asthma guidelines, be a well-planned and well-executed educational and therapeutic process (86). Previous research has shown that the transition from pediatric to adult healthcare is often haphazard, e.g., when the transition has not been planned appropriately (85, 89, 94, 95). Thus, there is a need for improved transition and services in all settings (96).

Two recent systematic reviews have highlighted that a structured transition process for adolescents with chronic conditions results in beneficial outcomes, such as satisfaction and adherence with care, and improved self-care skills (97, 98). Models for the transition from pediatric to adult healthcare have been developed for, e.g., congenital heart disease and diabetes type 1 (99, 100), but so far not for the large group of adolescents with asthma. The care of these diseases has similarities, but also differences. Most patients with asthma are managed in primary care, while those with heart disease or diabetes type 1 are managed in specialist care. However, for young adults with asthma, there is generally no main caregiver taking over responsibility after age 18 years. In a previous qualitative study, this was described as follows by one parent to an adolescent with severe allergic disease: *"Hello, 18 years and then, you're out. Goodbye! Then you get no more help"* (101).

Rationale for **Study II**

There was limited research in the field of asthma and the transition from pediatric to adult healthcare and in particular on young adults' experiences of the transition process when I began my research. Most qualitative studies to date when planning for **Study II** focused on the developmental transition and adolescents becoming independent (102-104). However, to improve the transition process, healthcare providers need to know how young adults with asthma experience their transitional care.

Rationale for **Study III**

Adolescents with asthma have an increased risk for asthma morbidity compared with younger children with asthma (89). One hypothesis used in planning for **Study III** was that drug utilization and healthcare consumption were adversely affected in the transition from pediatric to adult healthcare. In a healthcare setting, it is important to identify patients in need of further management and follow-ups, to prevent disease progress and guide adolescents in the transition to adult healthcare (31, 82).

2 Research aim

The overall research aim of this thesis was to characterize asthma in adolescence and young adulthood with a particular focus on sex and severity, and to identify factors of importance for improved asthma management during the transition from pediatric to adult healthcare.

2.1 Specific aims

- To characterize asthma in adolescence, in relation to sex and severity (**Study I**).

- To investigate management of adolescents and young adults with asthma during the transition from pediatric to adult healthcare (**Studies II** and **III**).

- To identify and characterize trajectories of asthma from infancy to young adulthood, and their associations with lung function and inflammatory and respiratory markers in adolescence and young adulthood (**Study IV**).

3 Material and methods

3.1 The BAMSE birth cohort

All four studies in this thesis were conducted within the ongoing Swedish population-based prospective birth cohort BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology) (105). The original aim of the BAMSE study was to investigate risk factors for asthma and other allergic diseases in childhood, and to study factors for prognosis of already established allergic disease in the general pediatric population. However, the scope has broadened with time.

3.1.1 Recruitment

The BAMSE project started in February 2004 with recruitment of new-born children from child health centers in four predefined areas in Stockholm: the municipalities in the northwest parts of the inner city, Solna, Sundbyberg, and Järfälla. The selected study areas included inner city, urban, and suburban districts, and represented different types of buildings and parental socioeconomic statuses (education and profession). Recruitment continued until November 1996. A community population register ensured that the parents of all infants born in the area during the recruitment period were contacted. Out of the 7,221 infants born during this period in the study areas, the parents of 477 could never be reached and 1,256 were actively excluded based on the exclusion criteria: the family planned to move within 1 year of the project start; insufficient knowledge of Swedish; the family had a seriously ill child; an older sibling was already included in the study (**Figure 4**). This left 5,488 eligible children, and of these, 502 declined participation, and 897 never answered the baseline questionnaire. The final cohort consisted of 4,089 children (49.5% girls), 75% of the eligible children, whose parents answered the baseline questionnaire when their children were a median age of two months.

To evaluate the representativeness of the included children in the BAMSE cohort, the actively excluded and non-responding families (n = 1,418) were sent a short questionnaire in 1996 with questions on details of family history of allergic disease, parental smoking, and the presence of furred pets in the household. The response rate to the questionnaire was 83% among the actively excluded and 58% among the non-responders. The results showed that family history of allergic disease and keeping of pets did not differ between the actively excluded or non-responding families compared with the included families. However, parental smoking was more prevalent among the actively excluded and non-responding families than among the included families. Thus, family history of allergic disease did not influence the motivation to participate, but lifestyle did.

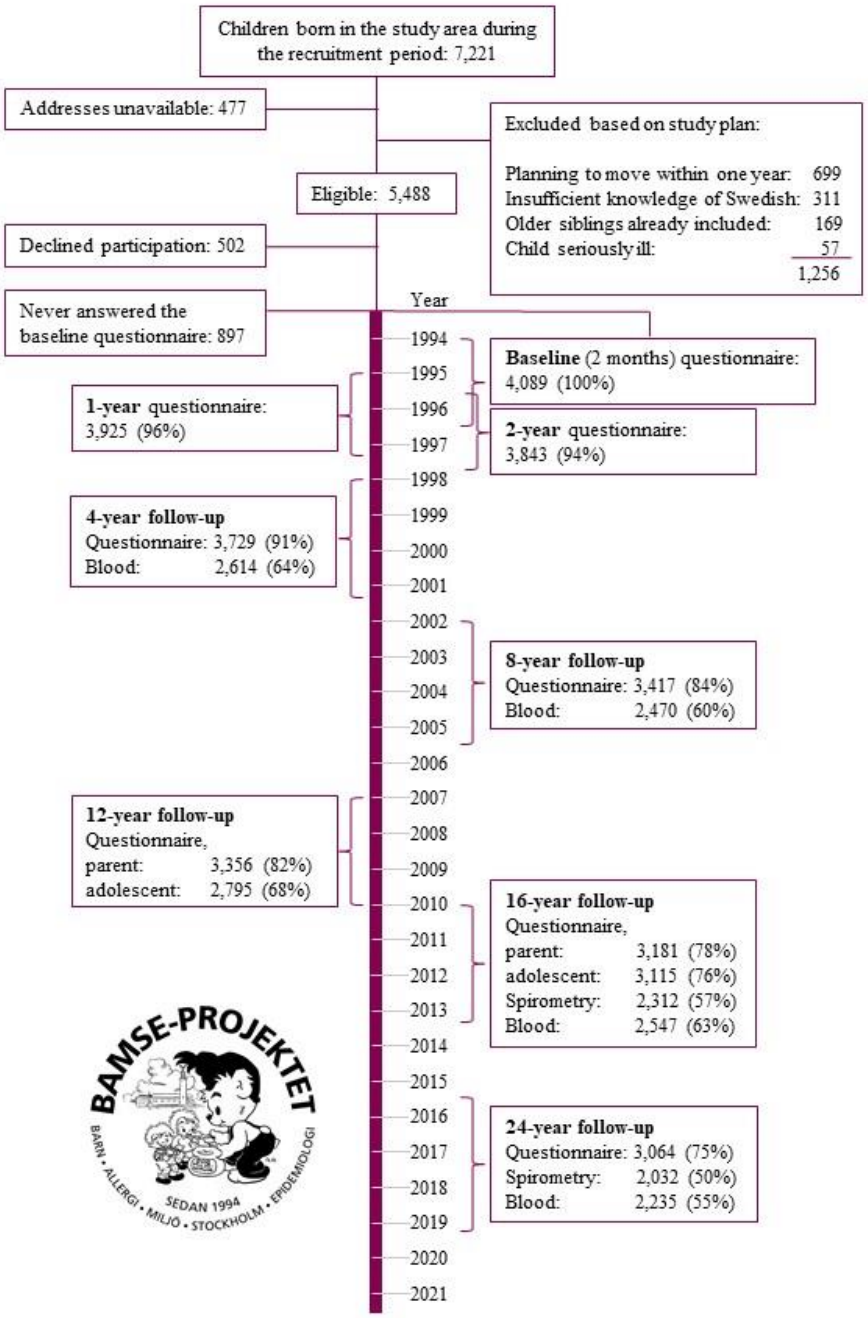

Figure 4. Flowchart of the recruitment and follow-up periods of the BAMSE cohort.

3.1.2 Questionnaires and clinical examinations

When the children were on average 2 months of age, a baseline questionnaire was used to collect information on background factors such as family history of allergic disease, parental education, and environmental and lifestyle factors. Follow-up questionnaires were distributed to parents when the participants were approximately 1, 2, 4, 8, 12, and 16 years old, to collect information about symptoms related to asthma and allergic diseases, lifestyle factors, and

treatment of asthma. Follow-up response rates were 96%, 94%, 91%, 84%, 82%, and 78%, respectively. In addition, at approximately 12 and 16 years, participants were asked to complete one questionnaire themselves. Follow-up response rates were 68% and 76%, respectively. At 24 years, the questionnaires were distributed only to the participants; the follow-up response rate was 75%. From age 12 years and onwards, most of the questionnaires were web-based. The questions in the questionnaires were, in so far as possible, harmonized with the International Study of Asthma and Allergies in Childhood (ISAAC) up to the 12-year follow-up, and thereafter with the MeDALL project (33, 106).

At ages 4, 8, 16, and 24 years, the participants were invited to undergo a clinical examination including for example blood sampling (described under **3.5.4**), measurements of lung function (**3.5.5**), height, and weight. The examinations were standardized and performed by trained nurses.

3.2 National and regional registers

To address the specific aims in this thesis, BAMSE data were linked to data from national and regional registers using personal identity numbers (107). A flowchart showing how BAMSE data from the 16- and 24-year follow-ups were linked to mandatory Swedish health registries between 2008–2018 is seen in **Figure 5**. In **Study I**, the research group had information on prescribed and dispensed asthma medications for each participant within the 18 months preceding the 16-year follow-up (based upon individual age). In **Studies II** and **IV**, the research group had information on prescribed and dispensed asthma medications for each participant within the 18 months preceding the 24-year follow-up (based upon individual age). In **Study III**, the research group used information regarding a period of eight years in total: four years before and four years after age 18 years, respectively (based upon individual age, participants born 1994–1996).

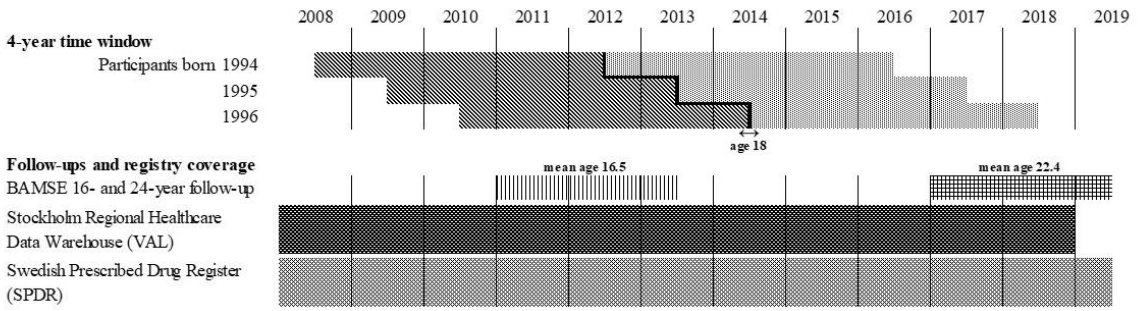

Figure 5. BAMSE data from the 16- and 24-year follow-ups linked to mandatory Swedish health registries between 2008–2018, with study periods for **Study III**.

3.2.1 Stockholm Regional Healthcare Data Warehouse

In **Study III**, data on asthma-related healthcare consumption were obtained from the Stockholm Regional Healthcare Data Warehouse, VAL (108). The register is held by Region Stockholm. The VAL database is a mandatory register, with both public and private care providers legally obliged to record diagnoses and report them to the authorities, with the exception of a few private clinics that do not receive subsidies (109). However, these clinics target the adult population rather than adolescents and young adults. Further, patients have the right to seek healthcare anywhere in the country, irrespective of which region they live in, based on agreements between the regions and the Ministry of Health and Social Affairs. In both primary and specialist care, there are user charges for healthcare consultations in the form of flat-rate fees (110, 111). However, under Swedish law, an individual will never pay more than 1,100 SEK (€120) per year for consultations. In region Stockholm, patients under 18 years of age are exempt from user charges (112). The VAL database includes complete data on all healthcare consultations in primary and specialist care, all hospitalizations and medical procedures, and diagnoses based on the International Statistical Classification of Diseases, version 10 (ICD-10) (113). For each healthcare consultation, a maximum of 15 diagnoses based on the ICD-10 can be registered. One diagnosis is assigned as the main condition, while others are secondary (110). The research group identified participants with physician-diagnosed asthma, ICD-10 codes J45 and/or J46, as their main or secondary diagnosis. To assess potential underreporting or misclassification of diagnoses, a sensitivity analysis was performed with all ICD-10 codes J – "Diseases of the respiratory system." With data linked to personal identity numbers, it was possible to follow each individual over time (107).

3.2.2 The Swedish Prescribed Drug Register

In all four studies in this thesis, information on dispensed asthma medications was obtained by linkage to the Swedish Prescribed Drug Register (SPDR) (107, 114, 115). Since July 2005, all drugs purchased at Swedish pharmacies are registered in the SPDR. The register is held by the National Board of Health and Welfare. The medications included were the following, classified in accordance with the Anatomical Therapeutic Chemical (ATC) Classification System (116): short-acting β_2-agonists, SABA (R03AC02 and R03AC03), LABA (R03AC12 and R03AC13), ICS (R03BA), fixed combinations of ICS and LABA (R03AK), and LTRAs (R03DC).

3.3 Qualitative concepts

Qualitative methods are often used when the aim is to improve knowledge with a focus on new insights and understanding (117-119), which was the specific aim of **Study II**. Data collection in qualitative research is usually achieved through interviews, with either focus groups or individuals (119). The method of participant recruitment is important, as this impacts on the variety of perceptions of the specific aim. Purposive sampling, i.e., an "appropriate selection," can yield a depth and width of data, which is important for internal validity (i.e., whether or not the study investigates what it is meant to) (118). The sample size in qualitative studies is often in the range 10–25 participants (117). An approximation of sample size is necessary for planning, while the sufficiency of the final sample size must be evaluated continuously during the research process (120). There are several different tools used to guide sample size, and a common concept in qualitative studies is "saturation," i.e., the required number of participants has been reached when new empirical data start to be similar to previous data (121). Another concept is "information power," which indicates that the more information the sample holds, the lower the number of participants that is needed (120). It is suggested that a sample with enough information power depends on the aim of the study, the sample specificity, the use of established theory, the quality of dialogue, and the analysis strategy.

In **Study II**, a qualitative approach was used to enable the research group to address the specific aim. Qualitative data were obtained through individual semi-structured (also called in-depth) interviews, a method chosen to gain rich and varied data to cover the aim of the study (118, 120). All interviews were audio-recorded, conducted in Swedish and were held in person or by telephone (due to geographical barriers for the participant).

An interview guide was developed based on joint discussions between the researchers about factors of importance for the interview, using previous knowledge as healthcare providers with clinical experience of asthma management (122). A preliminary interview guide was formulated and pilot-tested twice. The final, slightly revised, interview guide, supported by previous literature, centered on exploring young adults' experiences when transitioning from pediatric to adult healthcare, with a focus on expectations, needs, and responsibilities (123). The sequencing of the open-ended questions was not the same for each participant, as it depended on the individual's responses. Supplementary follow-up questions were asked if necessary, for clarification purposes.

3.3.1 Approaches for analyzing qualitative data

Depending on the aim of the study, there are various approaches for analyzing qualitative data (124). Common methods include: *Phenomenology* – describing the common meaning of experiences of a phenomenon for individuals. *Grounded theory* – developed by Strauss and Corbin, with a focus on a theory that explains some action, interaction, or process. *Ethnography* – studying an intact social group primarily based on long periods of observations. *Case study* – involves the study of a case within a real-world context or setting.

In **Study II**, the s*ystematic text condensation* (STC) approach, in accordance with Malterud (121), was used. STC is based on Giorgi's psychological phenomenological analysis with the ambition to develop knowledge of the informant's experiences and lifeworld (121). The research group used a non-theory-driven inductive procedure, starting from an individual level, gathering empirical data and then drawing conclusions. STC presents the experiences of the participants, as expressed by the participants themselves (121). STC provides intersubjectivity, reflexivity, feasibility, and a responsible level of methodological rigor (121). The analysis involves decontextualization and recontextualization (varying between parts and whole) (118) based on four steps:
Step 1, getting an overall impression of the text by reading the transcribed data and identifying preliminary themes.
Step 2, identifying meaning units in the preliminary themes by sorting out the text and keeping relevant text. Next, labelling with codes when sorting the meaning units related to the preliminary themes in step 1 – decontextualization of the results.
Step 3, sorting the codes by meaning, and further into subgroups.
Step 4, recontextualizing data and synthesizing the essence of each meaning from condensation to descriptions and concepts of each category (121).

3.3.2 Validating qualitative research

There are different ways of interpreting qualitative results, and the researcher must reflect on their preconceptions during the process and stay as neutral as possible to achieve *confirmability*. Further, the qualitative research process is validated through established concepts (125). The concepts *credibility*, *dependability* and *transferability* have been used to explain various aspects of *trustworthiness*: in what way can I describe and review the overall sustainability in the study? *Credibility*, describes the entire data collection process; can I follow the entire process? Did the authors choose the "right" participants – did they use the correct method? Do the participants have different experiences? Are there enough participants in the study to highlight the problem? *Dependability*, how reliable are the data?

How are the questions worded? Are the questions adjusted over time and how reliable are they after adjustment? *Transferability*, in what way can I transfer the results to other groups/patients? Is there a clear description of the context, selection, and characteristics of the participants, the data collection, and the analysis process?

3.4 Study populations

The four studies in this thesis had different study populations, depending on the specific aims and inclusion criteria.

The *study population* in **Study I** consisted of 3,115 adolescents (76.2% of the original cohort), who had answered the questionnaire at the 16-year follow-up.

The *study population* in **Study II** included young adults with asthma who had experience of living with asthma in adolescence and in young adulthood, and was chosen using a purposive sampling (118). Participants were recruited in two steps, based on information from the follow-ups at both 16 and 24 years. At 16 years, they were to have been classified as having asthma (n = 437) (**Table 1**). In addition, they were to have been dispensed high daily doses of ICS as ICS separately or as fixed combinations of ICS and LABA, in the 18 months preceding the follow-up (n = 104). At 24 years, they were to have had current respiratory symptoms in the preceding 12 months. In all, 30 individuals fulfilled these criteria according to data reported in the questionnaires between the start of the 24-year follow-up and February 2018. As an invitation to participate, a research nurse called the young adults fulfilling the above criteria and asked if the author of this thesis (M.Ö.) could contact them. M.Ö. thereafter contacted those who had consented. In total, 14 young adults were excluded due to no contact with healthcare before and after age 18 years (n = 4), not wanting to participate (n = 3), or not being reachable at ≥ three different timepoints (n = 7). In total, 16 young adults with severe asthma were included in the final analyses.

Table 1. Recruitment, fulfilled criteria and *study population* in **Study II**.

Follow-up	**Fulfilled criteria**	**Number (n)**
At age 16 years *and*	Asthma	437
	Dispensed high daily doses of ICS or ICS/LABA	104
At age 24 years	Current respiratory symptoms	30
Study population	Exclusion	14
	Interviews	16

In **Study III**, the *study population* consisted of all participants who responded to the questionnaires and lived in the Stockholm region at both the 16- and 24-year follow-ups (n = 1,808, 44.2% of the original cohort) (**Figure 6**). For analyses related to the clinical examinations, participants with a valid spirometry measurement were included.

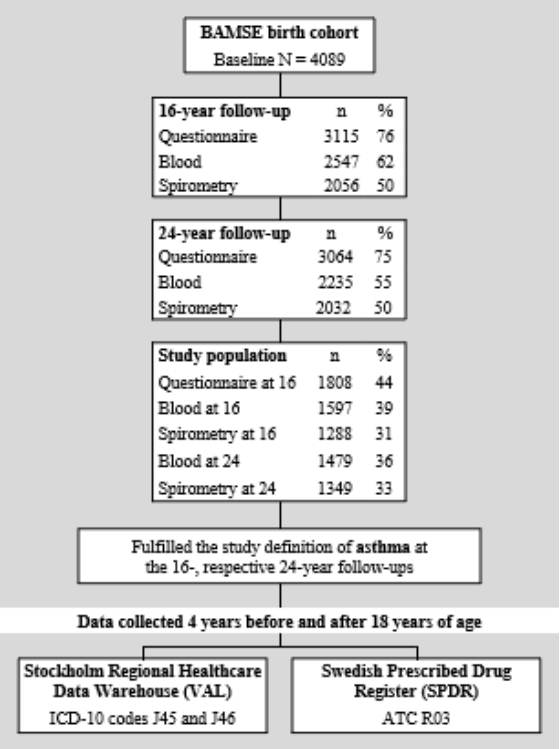

Figure 6. Flowchart of the *study population* (n = 1,808) and data sources for asthma-related healthcare consumption and pharmacological dispensation in **Study III**.

The *study population* in **Study IV** included the original BAMSE cohort of 4,089 participants.

3.5 Descriptions and definitions

As the focus in this thesis was on adolescents and young adults, it is appropriate to specify these terms. According to the WHO, adolescents are individuals in the 10–19-year age group, a phase of life between childhood and adulthood. Further, the WHO refers to "youths" as individuals in the 15–24-year age group, and "young people" as individuals in the age range 10–24 years. In this thesis, the term "adolescence" refers to the time of the questionnaire at the 16-year follow-up, where the age range among participants was 15.7–19.0 years (mean age 16.6 years). The term "young adulthood" refers to the time of the questionnaire at the 24-year follow-up, where the age range among participants was 21.5–25.2 years (mean age 22.5 years).

3.5.1 Background characteristics

Background characteristics were gathered from the baseline questionnaire answered by the parents when the children were about 2 months of age (**Table 2**).

Table 2. Definitions of background characteristics used in this thesis.

Variable	Definition	Study
Young maternal age	Mother's age below 25 years of age at birth of the child.	I, III, IV
Preterm birth	Gestational age < 37 weeks.	IV
Breastfeeding duration	Exclusive breastfed for ≥ 4 months.	IV
Older siblings	Any older siblings in the household/family at the time of baseline questionnaire.	IV
Family history of allergic disease	Mother and/or father with doctor's diagnosis of asthma and asthma medication and/or doctor's diagnosis of rhinitis in combination with reported allergy to furred pets and/or pollen at the time of baseline questionnaire.	I–IV
Furred pet at home	Had a furred pet (cat, dog, and/or rodent) at home at the time of baseline questionnaire.	IV
Higher parental education	Higher education – at least university or college degree/other education at the time of baseline questionnaire.	I, III, IV
Socioeconomic status	Dominant socioeconomic status for the household, dichotomized into blue (low) and white (high) collar worker. Based on the Nordic standard occupational classification and Swedish socio-economic classification (126).	I
Tobacco smoke exposure	Either of the parents smoked at least one cigarette per day at the time of baseline questionnaire.	I, III, IV
Parent born outside Sweden	Father and/or mother born outside of Sweden.	I, III, IV

3.5.2 Definitions of asthma and asthma phenotypes

Definitions of asthma were based on questionnaire data from all follow-ups. Age-specific definitions are described in **Table 3**. Parents reported up to the 8-year follow-up, and participants reported at the 12-, 16-, and 24-year follow-ups.

Phenotypes of asthma were defined with respect to clinical parameters (persistent asthma), immunological parameters (allergic asthma), age at onset (hypothesis-based adolescent-onset and persistent asthma), response to medication (asthma control), and severity of disease (asthma with high daily doses of ICS, severe asthma) (**Table 3**).

Four alternative variants of asthma control were included in the definition of severe asthma. However, the asthma control variant used in **Studies I**, **III**, and **IV** was based on the modified GINA definition (**Table 3)**.

Table 3. Definitions of asthma and asthma phenotype used in this thesis.

Variable	Definition	Study
Asthma at age 1, 2, 4, 8, 12, 16, and 24 years	Fulfilling at least two of the following three criteria: Symptoms of wheeze and/or breathing difficulties in the preceding 12 months, ever doctor's diagnosis of asthma, and/or use of any asthma medication occasionally or regularly in the preceding 12 months.	I–IV
Persistent asthma	Fulfilling the definition of asthma at both the 16- and 24-year follow-ups.	III
Allergic asthma at age 16 and 24 years	A combination of asthma and IgE sensitization to inhalant allergens (cat, dog, horse, and/or house-dust mite, timothy grass, birch, mugwort, and/or mold) at the 16- and 24-year follow-ups.	III
Asthma control at age 16 and 24 years	Symptoms based on the modified GINA definition (1), which included: at least 4 episodes of wheeze, any night-time awakening, activity limitation, and use of a symptom reliever at least 2 times/week in the 12 months preceding the 16- and 24-year follow-ups. Having none of the symptoms was defined as controlled asthma; having at least 1 of 4 symptoms was defined as uncontrolled asthma.	I, III, IV
Asthma with high daily doses of ICS at age 16 and 24 years	Dispensed at least 800 µg budesonide or equivalent (≥ 500 µg fluticasone), as ICS separately or as fixed combinations of ICS and LABA within the 18 months preceding the 16- and 24-year follow-ups.	I–IV
Severe asthma at age 16 and 24 years	Based on ERS/ATS and GINA guidelines (1, 73). Defined as asthma with *high daily doses of ICS* plus dispensed LABA (together with ICS separately) and/or LTRA at least once in the 18 months preceding the 16- and 24-year follow-ups to prevent the asthma from becoming or remaining uncontrolled despite therapy. Uncontrolled asthma was defined as at least one of the following four alternatives based on symptoms in the 12 months preceding the 16-year follow-up: (1) *Uncontrolled asthma* as defined above (modified GINA); (2) Taken cortisone tablets dissolved in water for asthma or respiratory symptoms ≥ 3 days in a row in the 12 months preceding the 16- or 24-year follow-ups; (3) Sought acute medical care because of respiratory symptoms in the 12 months preceding the 16- or 24-year follow-ups; and (4) Impaired lung function, FEV_1 below 80% of predicted, measured through spirometry at the 16- or 24-year clinical follow-ups.	I, III, IV
Age at onset, hypothesis-based		
Adolescent-onset asthma	Fulfilling the criteria for asthma at 12 or 16 years, but not at earlier ages.	I
Persistent asthma	Fulfilling the criteria for asthma at 12 or 16 years and at least 1 previous occasion at earlier ages (1, 2, 4, or 8 years of age).	

3.5.3 Health outcomes besides asthma

Health outcomes besides asthma were based on questionnaire data from the follow-ups at approximately 4, 8, 16, and 24 years of age. Parental responses were used up to the 8-year follow-up, and at the 16-year follow-up, data were based on the participants' answers when possible. Age-specific definitions are described in **Table 4**.

Table 4. Definitions of health outcomes besides asthma used in this thesis.

Variable	Definition	Study
Eczema		
At age 4 years	Parental report of dry skin and itchy skin rash for ≥ 2 weeks in specific locations (face or arm/leg extension surfaces or arm/leg flexures or wrist/ankle flexures) within the preceding 12 months and/or doctor's diagnosis of eczema after 2 years and up to the date of the 4-year questionnaire.	IV
At age 8 years	Parental report of dry skin and itchy skin rash for ≥ 2 weeks in specific locations (face or arm/leg flexures or wrists/ankles or neck) within the preceding 12 months and/or doctor's diagnosis of eczema after 4 years of age up to 8 years of age.	
At age 16 years	Adolescent-reported dry skin and itchy skin rash in specific locations (arm/leg flexures or wrists/ankles or neck) within the preceding 12 months.	II, IV
At age 24 years	Participant's report of itchy rash in the preceding 12 months in combination with 3 out of 4 of the following criteria: 1) Dry skin in the preceding 12 months. 2) Eczema onset below age 2 years. 3) history of flexural eczema at any follow-up. 4) Personal history of asthma and/or rhinitis at any follow-up from age 4 years.	IV
Rhinitis		
At age 4 years	Parental report of symptoms from eyes/nose (suspected or evident) after exposure to furred pets or pollen (after age 2 years) and/or doctor's diagnosis of allergic rhinitis after 2 years and up to the date of the 4-year questionnaire.	IV
At age 8 years	Parental report of symptoms of sneezing, a runny or blocked nose, or itchy, red and watery eyes after exposure to furred pets or pollen (from age 4 years) and/or doctor's diagnosis of allergic rhinitis from 4 years and up to the date of the 8-year questionnaire.	IV
At age 16 years	Parental report of symptoms of sneezing, a runny or blocked nose, or itchy, red, and watery eyes after exposure to furred pets or pollen (preceding 12 months) and/or doctor's diagnosis of allergic rhinitis from the age of 12 years up to the date of the 16-year questionnaire.	II, IV
At age 24 years	Participant's report of symptoms of sneezing, a runny or blocked nose, or itchy, red and watery eyes after exposure to furred pets or pollen (preceding 12 months) and/or doctor's diagnosis of allergic rhinitis ever up to the date of the 24-year questionnaire.	IV

Continuing **Table 4**.

Variable	Definition	Study
BMI status at age 16 years	Based on data from the 16-year clinical examination. Calculated as kg/m^2 and categorized into thinness/normal weight or overweight/obese, based on age-specific cut-off values from the International Obesity Task Force (127).	I
Age of puberty at age 16 years	Based on self-reported information from the 16-year follow-up on first menarche for females and voice change for males.	IV
Current smoking at age 16 years	Adolescent-reported occasional current smoking at the time of 16-year follow-up.	I
Respiratory markers	*"> 12 episodes of breathing difficulties"* and "*respiratory symptoms following physical exertion"* were based on self-reported information in the 12 months preceding the 16- and 24-year follow-ups.	IV

3.5.4 Blood sampling

Blood sampling was performed at the clinical examinations at the 4-, 8-, 16-, and 24-year follow-ups (**Figure 4**). Analyses were performed of, among other things, blood serum IgE and the results were used in all four studies in this thesis. IgE sensitization to common inhalant and food allergens was analyzed using the ImmunoCAP System (Thermo Fisher/Phadia AB, Uppsala, Sweden) with Phadiatop® (cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus*/house dust mite, and *Cladosporium herbarum*/mold), and fx5® (cow's milk, peanut, hen's egg, wheat, soybean, and fish). In **Study I**, inhalant allergens were further categorized into indoor allergens – cat, dog, horse, and/or house dust mite – and outdoor allergens – timothy grass, birch, mugwort, and/or mold. IgE values greater than 0.35 kU_A/L were regarded as positive.

In **Study I** and **IV,** analyses of eosinophils and neutrophils (performed at the Department of Clinical Chemistry, Karolinska University Hospital, Stockholm, Sweden) were also used. Values for blood eosinophil cell count were regarded as high if > 0.5 (10^9 cells/L), for all ages in **Study I** (128, 129). In **Study IV**, values for blood eosinophil cell count were regarded as above reference if ≥ 0.3 (10^9 cells/L), for all ages. Values for blood neutrophil cell count were regarded as high if > 8.0 (10^9 cells/L) for < age 18 years, and > 7.5 (10^9 cells/L) for ≥ age 18 years in **Study I**. In **Study IV**, values for blood neutrophil cell count outside normal were based on the highest tertile (tertile 3) (130): > 3.9 (10^9 cells/L) for 16-year data and > 4.1 (10^9 cells/L) for 24-year data.

3.5.5 Lung function

In **Studies I, III,** and **IV,** lung function measurements were performed through spirometry using a Jaeger MasterScreen-IOS system (Carefusion Technologies, San Diego, CA, USA) at the 16- and 24-year clinical follow-ups (**Figure 4**). All subjects performed repeated maximal expiratory flow volume measurements (MEFV) (131, 132). The MEFV curves were manually inspected and deemed acceptable if the two highest values of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were reproducible according to the ERS/ATS criteria (133, 134). FEV_1 refers to the maximal volume of air exhaled in the first second of the forced expiration (the ability to exhale quickly). FVC measures the maximal volume of air exhaled with maximally forced effort from a full inspiration (the size of the lung). The ratio between FEV_1/FVC is used to define airflow obstruction and a ratio under 0.7 is usually used as a cut-off value in adults (1). With reversibility testing, pre- and post-results are compared after inhalation of a bronchodilator, and an increase in FEV_1 of > 12% and > 200 ml from baseline is an indicator of asthma in adults.

Global lung function initiative (GLI) reference values were used to obtain predicted lung function values and corresponding standard deviation scores (z-scores) (135). GLI reference values provide a robust reference standard to rationalize the interpretation of spirometry results within and between populations worldwide. With reference values, sex, age, height, and ethnicity can be taken into account, meaning that a predicted value or a lower limit of normal (LLN) for an individual can be calculated (135). The variable airflow obstruction/limitation was defined as a FEV_1/FVC ratio below the LLN, in turn defined as the lower 5^{th} percentile in the never-asthmatic population.

3.5.5.1 Fractional exhaled nitric oxide

In **Studies I** and **IV**, fractional exhaled nitric oxide (FeNO) was investigated and a value ≥ 25 parts per billion (ppb) was deemed to indicate the presence of eosinophilic inflammation. FeNO was performed at an expiratory flow of 50 mL/s ($FeNO_{50}$), using an online chemiluminescence analyzer (at the 16-year follow-up, EcoMedics Exhalyzer®, and at the 24-year follow-up, Circassia NIOX VERO®). The procedure was performed in accordance with published guidelines (131, 136).

3.6 Statistical analyses

All statistical analyses in this thesis were performed using the STATA statistical software (release 14.2; College Station, TX, USA). The main statistical methods used in **Studies I, III, and IV** to study whether there were differences between groups were the chi-squared test (Fisher's exact test when sample sizes were small, expected numbers < 5), and tests of proportion for categorical/dichotomous variables. The non-parametric analysis Wilcoxon signed-rank test was used to study differences before and after age 18 years, and the two-sample Wilcoxon rank-sum test was used to study sex differences in **Study III**. McNemar's test was used on paired nominal data to evaluate differences in asthma control over time in **Study III**. One-way analysis of variance (ANOVA) was used to compare means of variables in **Study IV**. P-values of < 0.05 were considered statistically significant.

The main statistical methods used in association analyses were logistic regression for categorical/dichotomous outcome variables, and multinomial logistic regression was used when the outcome variable consisted of more than two categories. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Linear regression was used for continuous outcome variables and results were expressed as mean values with 95% CI. Potential confounders were selected *a priori* from the previous literature and included in the regression models. Sex, co-morbidity, age at onset of asthma, lung function, and eosinophil count, which are described in the background section, are known to be associated with asthma. Socioeconomic status/parental education (which can be defined in different ways, e.g., based on occupation, income, and/or education) is also known to be associated with asthma, reflecting lifestyle differences, such as infections, obesity (BMI status), exposure to allergens (IgE), exposure to tobacco smoking, and access to healthcare (1). Such lifestyle differences are known to be separately associated with asthma.

The logistic regression in **Study I** investigating the associations between sex and clinical characteristics on asthma control, was adjusted for sex (females vs. males), age at onset of asthma (persistent vs. adolescent-onset asthma), indoor or outdoor allergens (yes vs. no), rhinitis (yes vs. no), BMI status (overweight/obese vs. thinness/normal weight), adolescent's current smoking (yes, at least occasionally vs. no), lung function (FEV_1 below vs. above 80% of predicted), and high blood eosinophil cell count (above vs. below the reference 0.5 x 10^9 cells/L). Further, in **Study I**, a multinomial logistic regression investigating the association between age at onset of asthma and sex was adjusted for socioeconomic status (white vs. blue collar), parental allergic disease (yes vs. no), and parental smoking at baseline (yes vs. no).

The logistic regression in **Study III** investigating the association between having had an asthma-related healthcare consultation after age 18 years and asthma phenotype (allergic asthma, asthma and airflow obstruction, asthma with high daily doses of ICS, and severe asthma), was adjusted for sex (females vs. males) and socioeconomic status (blue vs. white collar worker).

The linear regression in **Study IV** investigating differences between mean values of lung function volume, was adjusted for sex (females vs. males), height, age, and weight at the 16- and 24-year follow-ups, respectively.

A LCA was performed to investigate trajectories of asthma in **Study IV**. Data on current asthma were included from all follow-ups (1-, 2-, 4-, 8-, 12-, 16-, and 24-year follow-ups). The R software (version 4.0.2) and package "depmixS4" was used. The models were compared for goodness-of-fit using the Bayesian information criterion (BIC) and the number of clusters was confirmed. A sensitivity analysis was also performed in the same way, but this included current asthma only up to the 16-year follow-up.

3.7 A summary of the four studies in this thesis

Study	**I**	**II**	**III**	**IV**
Study design	Observational study	Qualitative study	Observational study	Observational study
Study population	n = 3,115	n = 16	n = 1,808	N = 4,089
Data source(s)	Questionnaires at the baseline, 1-, 2-, 4-, 8-,12-, and 16-year follow-ups, and clinical examination at the 16-year follow-up. Register	Individual interviews	Questionnaires at the baseline, 12-, 16-, and 24-year follow-ups, and clinical examinations at the 16-, and 24-year follow-ups. Registers	Questionnaires at the baseline, 1-, 2-, 4-, 8-, 16-, and 24-year follow-ups, and clinical examinations at the 4-, 8-, 16-, and 24-year follow-ups. Register
Study period	2010–2013	N/A	2010–2019	1994–2019
Data analysis	Descriptive Logistic regression	STC	Descriptive Logistic regression	Descriptive Linear regression LCA

3.8 Ethical considerations

All four studies within the thesis were performed in accordance with the ethical principles of the Declaration of Helsinki (137). Informed consent was provided by the guardians, adolescents, and young adults, depending on the age at follow-up. Participants in the project were informed that they were free to withdraw from the study at any stage, and individual-level data would be deleted. At the 16- and the 24-year follow-ups, the participants were given a gift certificate of 500 SEK for participating in the clinical examination, as compensation for time lost and any inconvenience. The participants have received feedback on test results from the clinical examinations, and if results were abnormal, advice on seeking an appropriate level of care.

In **Study II**, a research nurse called the young adults as an invitation to participate in the study, and asked if the author of this thesis (M.Ö.) could contact them, to avoid making them feel compelled to participate.

The four studies in this thesis were approved by the Regional Ethical Review Board in Stockholm, Sweden. Register numbers for the permits are:

Study I: 93:189 and 2010/1474-31/3

Study II: 93:189, 2016/1380-31/2, 2016/2475-32, and 2017/395-32

Study III: 93:189, 2010/1474-31/3, 2016/1380-31/2, and 2016/2475-32

Study IV: 93:189, 98-175, 02-420, 2010/1474-31/3, 2016/1380-31/2, and 2016/2475-32

4 Results

4.1 Characterizing asthma in relation to sex

To characterize asthma in adolescence, the research group first investigated the prevalence of asthma in **Study I** and found that 14.2% (n = 437) fulfilled the study definition. Asthma tended to be more common among females than males (15.0% vs. 13.4%, p = 0.22). Further, age at onset of asthma, using the hypothesis-based approach, showed that 38.1% had adolescent-onset asthma and 61.9% had persistent asthma. Females had adolescent-onset asthma more often than males (45.3% vs. 30.0%, p = 0.01). The proportion of clinical characteristics among males and females with asthma in adolescence was also investigated in **Study I**. The majority of the adolescents with asthma were IgE-sensitized to inhalant allergens (79.9% males vs. 62.6% females, p < 0.01; **Figure 7**). Uncontrolled asthma was common – 46.2% of the adolescents with asthma had an uncontrolled disease – and more common among females than males (51.6% vs. 40.1%, p = 0.02). Further, in **Study I**, investigations of the distribution of uncontrolled asthma among adolescents with severe asthma compared with those with non-severe asthma showed a higher proportion of uncontrolled asthma among those with severe asthma (79.2%, vs. 53.0%, p = 0.01). In **Study III**, among the participants with persistent asthma (asthma at both the 16- and 24-year follow-ups), uncontrolled asthma was present among 57% (80 of 147) at the 16-year follow-up and among 72% (103 of 147) at the 24-year follow-up (p < 0.01). In the adolescent-onset and persistent asthma trajectory groups, based on the hypothesis-free trajectories in **Study IV**, 53.7% and 52.4%, respectively, had an uncontrolled disease at 24 years of age.

To enable comparison of asthma in adolescence and young adulthood, additional data were gathered to characterize asthma based on a study population that consisted of the 3,064 young adults who answered the questionnaire at the 24-year follow-up. In total, 14.0% (n = 429) fulfilled the study definition of asthma, see **Figure 7**. Asthma was more common among females than males (15.5% vs. 12.3%, p = 0.01). The proportion with IgE sensitization to inhalant allergens was 79.2% among males and 67.2% among females, p = 0.02. In this age group, uncontrolled asthma was common: 74.0% had an uncontrolled disease (71.7% males vs. 75.5% females, p = 0.39).

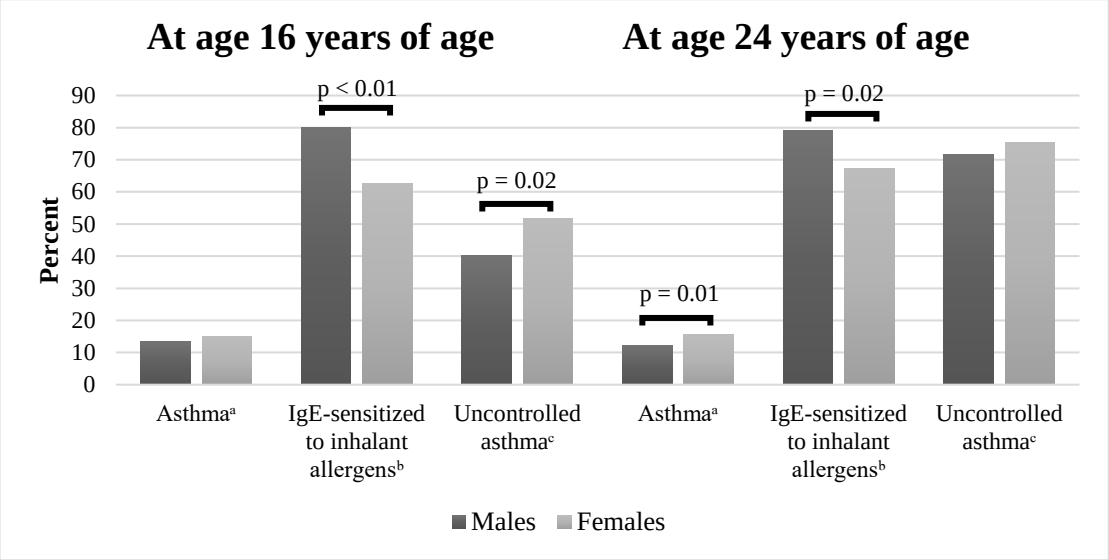

Figure 7. The proportions with asthma and the clinical characteristics among males and females with asthma at age 16 years (n = 437) and age 24 years (n = 429), respectively.

4.2 Asthma severity categorized based on pharmacological treatment

Investigating severity of asthma based on pharmacological treatment in **Study I** showed that a total proportion of 23.8% (n = 104) of the adolescents with asthma had been dispensed high daily doses of ICS or fixed combinations of ICS and LABA within the 18 months preceding the 16-year follow-up (**Figure 8**). This was more common among males than females (29.1% vs. 19.2%, p = 0.02). Moreover, 6.7% (n = 24) had severe asthma (6.1% females vs. 7.4% males, p = 0.61).

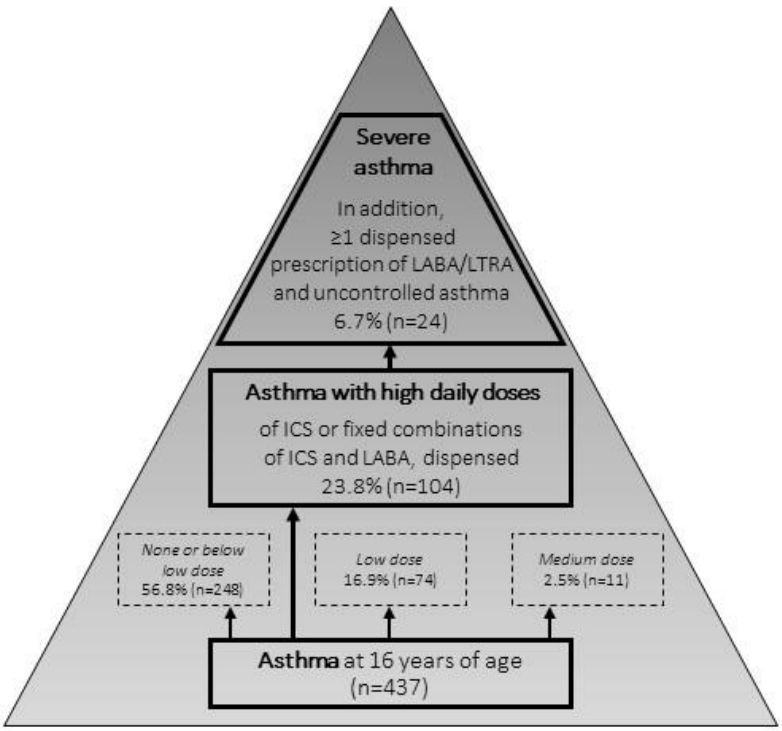

Figure 8. Asthma categorized by pharmacological treatment at age 16 years.

To gain additional data for this thesis, investigations were also performed of asthma severity based on pharmacological treatment in young adulthood. This was based on the study population encompassing 3,064 young adults. In total, 12.6% (n = 54) of the young adults with asthma had been dispensed high daily doses of ICS or fixed combinations of ICS and LABA within the 18 months preceding the 24-year follow-up. This was more common among females than males, although not statistically significantly (14.3% vs. 10.1%, p = 0.19). Moreover, 3.1% (n = 12 young adults; 10 females and 2 males) fulfilled the definition of severe asthma.

In **Study IV,** based on the hypothesis-free trajectories, it was found that severe asthma at 16 and 24 years of age was most prevalent in the adolescent-onset asthma trajectory group, albeit quite uncommon (n = 8, 4.1% at 24 years of age).

4.3 Asthma trajectories

Based on a hypothesis-free approach in **Study IV**, four asthma trajectories from infancy to young adulthood were identified. Class 1 had a predominant profile of never/infrequent asthma (n = 3,291, 80.4%) (**Figure 9**). Class 2 had a predominant profile of early-onset transient asthma, with debut of asthma at 1, 2, or 4 years of age, but no asthma in later years (n = 307, 7.5%). Class 3 had a predominant profile of adolescent-onset asthma with a debut of asthma after age 8 years (n = 261, 6.4%). Class 4 encompassed participants with predominantly persistent asthma (n = 230, 5.6%).

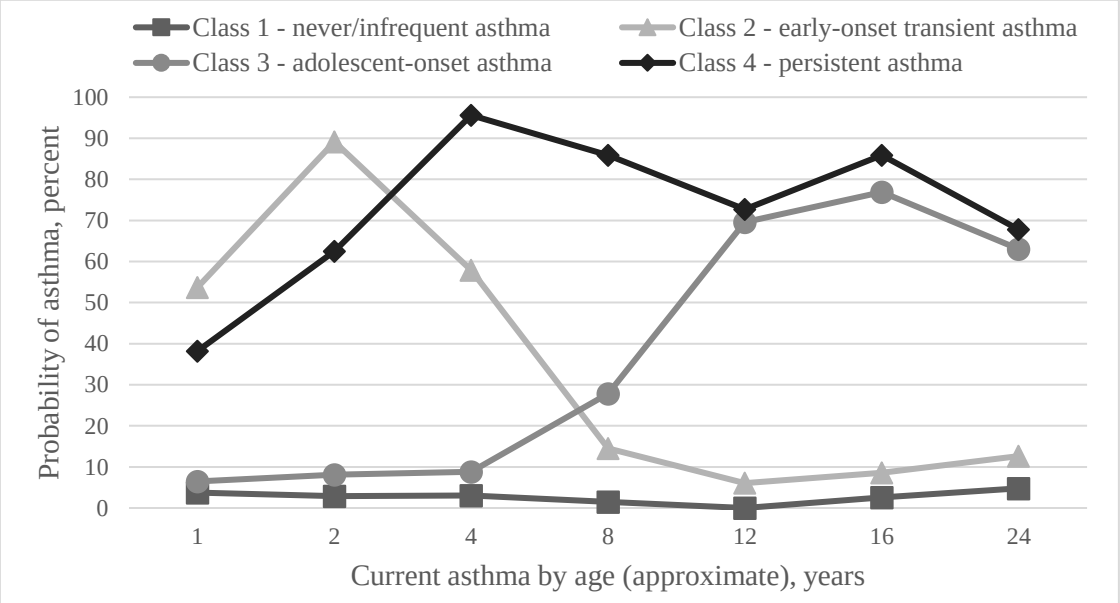

Figure 9. Trajectories of asthma from infancy to young adulthood using LCA (N = 4,089).

Characterizing the trajectories, the adolescent-onset asthma trajectory group was found to have the highest proportion of females (n = 148, 56.7%) and the persistent asthma trajectory group the lowest (n = 92, 40.0%). The early-onset transient asthma trajectory group showed the lowest proportion of participants who had been breastfed (n = 219, 73.2%). The highest proportion of parental smoking (n = 82, 26.7%) was seen in the same trajectory group. Higher proportions of having any older siblings and having a furred pet at baseline were also seen in the early-onset transient asthma trajectory group. In the persistent asthma trajectory group, 47.8% (n = 107) had a family history of allergic disease.

Moreover, sensitization to inhalant allergens increased with age in all trajectories, 75.0% (n = 135) of those in the adolescent-onset trajectory group and 71.3% (n = 82) of those in the persistent asthma trajectory group were sensitized to inhalant allergens at age 24 years. Further, the proportion of allergic comorbidity was highest in these trajectory groups; about one third had eczema at age 4 years and about two thirds had rhinitis at age 24 years. Sensitization to food allergens was most common in the persistent asthma trajectory group (n = 60, 35.3% at 4 years of age).

A separate comparison between the adolescent-onset and persistent asthma trajectory groups showed that there were few statistically significant differences with respect to respiratory markers, such as severe asthma and asthma control, at 16 or 24 years of age. However, the persistent asthma trajectory group had lower mean values of FEV_1 and FEV_1/FVC compared with the adolescent-onset group, as well as a higher proportion of airflow limitation (18.1% and 10.3%, p = 0.05) at age 16 years, a lower mean value of FEV_1, and a higher proportion of eosinophils (31.0% vs. 18.5%, p = 0.02) at age 24 years. Further, the persistent asthma trajectory group had the highest proportions of FeNO values ≥ 25 ppb at both 16 and 24 years of age (41.7% and 34.3%, respectively).

4.4 The transition from pediatric to adult healthcare

4.4.1 Experiences

In the qualitative analyses in **Study II**, important aspects of the included participants' experiences of the transition from pediatric to adult healthcare were identified. In total, four categories emerged during the analysis process: "I have to take responsibility," "A need of being involved," "Feeling left out of the system," and "Lack of engagement" (**Figure 10**).

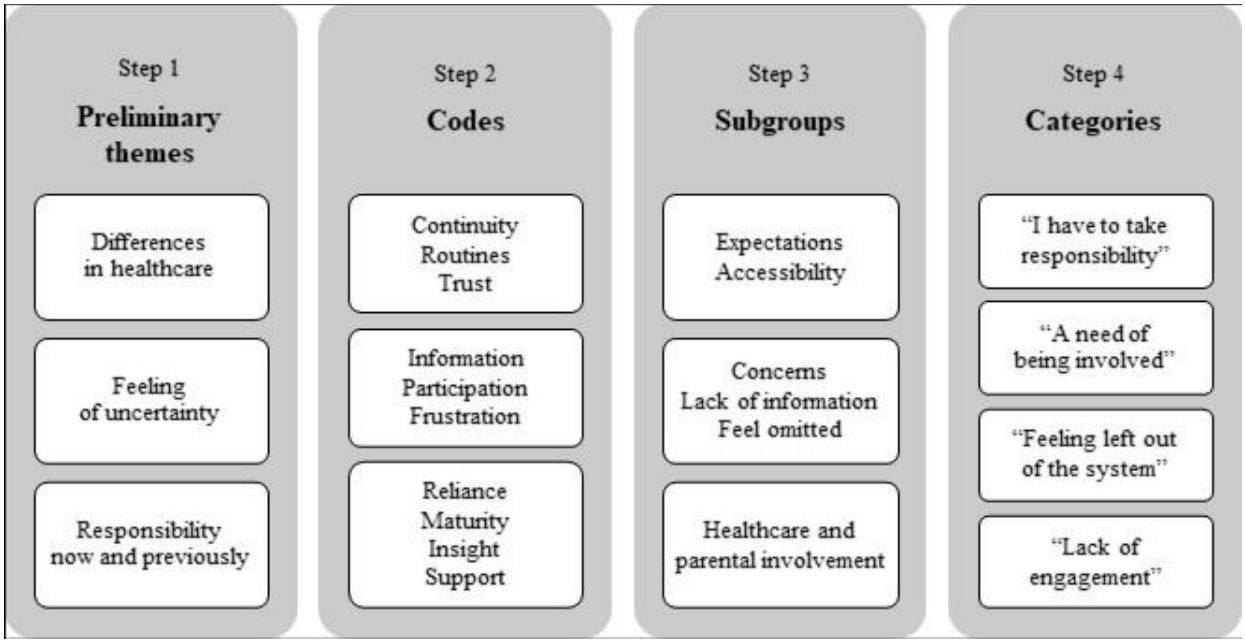

Figure 10. The analysis process in STC, steps 1–4.

Category – "I have to take responsibility"

After the transition to adult healthcare, the young adults expressed that they had to take more responsibility. They felt that they needed to be mature enough to take on full responsibility; it was up to the individuals to handle everything and to keep in touch with healthcare. The young adults' responsibilities included requesting care and taking their own asthma seriously.

> *"Just because you turn 18 and become an adult on paper, that doesn't mean that you are fully educated and mature enough to take on all the responsibility that it implies." (# 8)*

Category – "A need of being involved"

The young adults had not been aware that a transition from pediatric to adult healthcare was going to occur, and they wished that the healthcare providers had involved them in the process. Moreover, the young adults wanted a joint preparation for adult healthcare so that they, as young adults, would be more prepared, which would help them understand their asthma management.

> *"It's good if the center provides information that we are not responsible for you anymore and we will be referring you on, so that it's not just a final check-up and you leave and think that you'll be going back there again." (# 6)*

Category – "Feeling left out of the system"

The information about the transition had been lacking, and the young adults did not know where to turn for, e.g., a renewed prescription, and what the next step was. Moreover, they experienced fewer follow-ups than before, or none at all, whether or not a transition had occurred. Also, in the pediatric asthma/allergy clinic, the young adults had been familiar with their healthcare providers, but this was no longer the case after the transition, and visits became impersonal.

> *"It was really easy when I had a pediatrician. I just went there or called and they'd say that I could come in and then I could just barge in there and… So that was really easy. I got to know him. Now it's like okay, where should I go, what do I do, who do I call and so on. So that part is a bit more difficult now." (# 4)*

Category – "Lack of engagement"

The visits tended to come to nothing in adult healthcare, partly because they were often focused on a renewed prescription and no discussion or evaluation of the treatment; therefore, the visits did not feel important. Moreover, the young adults felt that their asthma in general received insufficient support from healthcare providers, compared with other chronic diseases. They felt that asthma was underestimated, and this feeling increased with time. For their part, the young adults viewed their asthma as something that affected their way of life during their most formative years and that had a big impact on them.

> *"Asthma is something that affects your way of life, in a way, during your most important formative years. It has quite a big impact." (# 8)*

4.4.2 Asthma-related healthcare consultations

Asthma-related healthcare consultations during the transition from pediatric to adult healthcare were investigated in **Study III**. In total, the study covered an 8-year period, extending 4 years before and 4 years after age 18 years. This period is hereafter denoted "before and after age 18 years." During the 4 years before age 18 years, 39% (58/147) of the young adults with persistent asthma (8.1%, n = 147; current asthma at both the 16- and 24-year follow-ups) had ≥ 1 asthma-related healthcare consultation; similar to the figure of 37% (55/147) for the 4-year period after age 18 years. Only 2% (3/147) had yearly healthcare consultations during the entire study period of eight years. The mean number of consultations decreased from 1.6 before age 18 years to 1.0 after age 18 years (p = 0.02).

Figure 11 shows the number of healthcare consultations before and after age 18 years, respectively, among participants with persistent asthma, divided by level of care. The most common combination was having no healthcare consultation either before or after age 18 years, and the second most common was attending specialist care before age 18 years, but having no healthcare consultation after age 18 years. After age 18 years, the mean number of healthcare consultations in primary care increased significantly and the number in specialist care decreased.

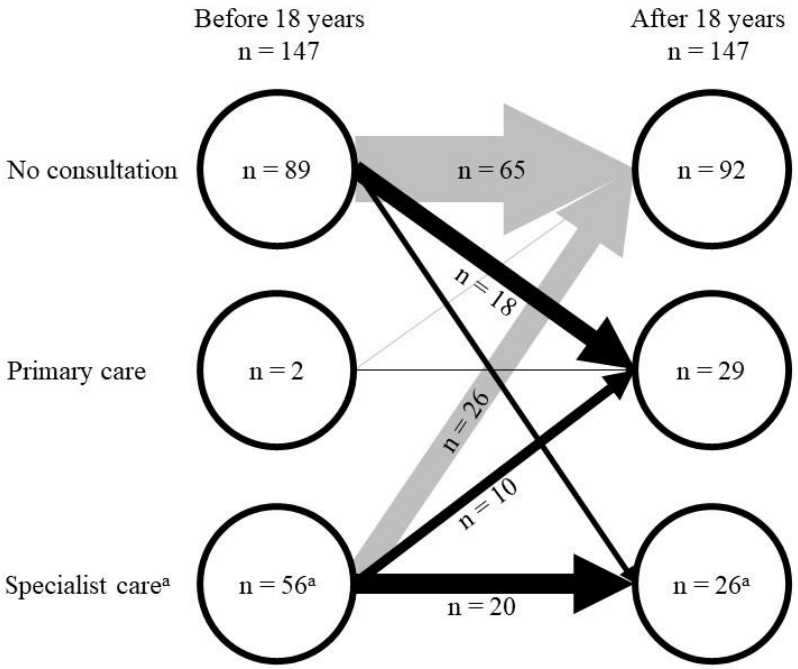

Figure 11. Number of healthcare consultations during the 4 years before and after age 18 years, respectively, divided by level of care, among young adults with persistent asthma (n = 147).
[a]Healthcare consultations in both primary and specialist care were merged into specialist care (n = 4).

Figure 12 shows the prevalence of current asthma among the participants with persistent asthma, and the mean number of yearly healthcare consultations in relation to sex.

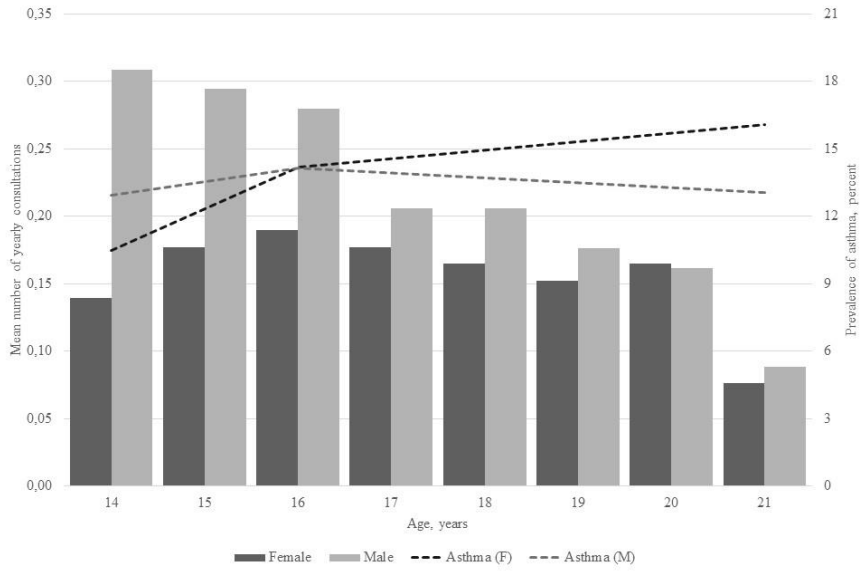

Figure 12. The mean number of yearly consultations among young females (n = 79) and males (n = 68) with persistent asthma and the prevalence of asthma during this period. The prevalence of current asthma is plotted based on prevalence at the 12-, 16-, and 24-year follow-ups.

Males had a higher mean number of healthcare consultations before age 18 years (males: 2.1, females: 1.2, p = 0.25), but after age 18 years, no difference was seen (males: 0.9, females: 1.1, p = 0.90). In regard to the registered healthcare consultations, medical procedures were also investigated; the mean number of registered spirometry tests among the participants with persistent asthma decreased from 0.27 before age 18 years to 0.16 after age 18 years (p < 0.01). More than 1 spirometry was registered among 27% (40 of 147) of the young adults before age 18 years and among 16% (24 of 147) after age 18 years.

4.4.3 Asthma-related pharmacological dispensation

Asthma-related pharmacological dispensation during the transition from pediatric to adult healthcare was investigated in **Study III** (in total, an 8-year period extending 4 years before and 4 years after age 18 years, respectively). Results showed that among those who fulfilled the criteria for persistent asthma (8.1%, n = 147; current asthma at both the 16- and 24-year follow-ups), at least one dispensation of reliever medication (SABA) was found for 70% (103/147) before age 18 years compared with for 50% (73/147) after age 18 years. The average number of dispensations was 2.8 before age 18 years and 2.1 after age 18 years (p <

0.01). Only 3% (4/147) had a regular dispensation of SABA once a year during the entire study period of eight years. As regards controller medication, at least one dispensation of any ICS (including ICS and fixed combinations of ICS and LABA) was found for 73% (107/147) before age 18 years, compared with for 50% (74/147) after age 18 years. The mean number of dispensations of any ICS was 3.1 before age 18 years and 2.1 after age 18 years ($p < 0.01$). During the entire eight-year period, only 3% (5/147) had a regular dispensation of any ICS once a year.

5 Discussion

5.1 Main findings and interpretations

5.1.1 Asthma prevalence and characteristics

Asthma during childhood is a broad term. This thesis has provided up-to-date results on the prevalence of asthma in the transitional period between childhood and adulthood within the general population. The asthma prevalence rates were assessed using standardized methods and required the presence of self-reported symptoms during a set period (the preceding year at each follow-up), as many asthmatics have intermittent symptoms and may not have them on the day of study (138). As regards asthma characteristics, the results of **Study I** showed a higher proportion of females than males with defined asthma at age 16 years, which highlights the natural course of asthma and is a clear manifestation of the "sex shift" in asthma prevalence (23). In **Study IV**, the adolescent-onset asthma trajectory group had the highest proportion of females, also highlighting the sex difference in age at onset of disease (139, 140). The results showed that uncontrolled asthma was more common among females than among males in adolescence and young adulthood. It has been proposed that asthma is underdiagnosed, undertreated, and more severe among females, and the later onset may lead to it not being properly identified in healthcare (23, 141). **Study III** also indicated potential undertreatment among females, as it was found that males had a higher mean number of healthcare consultations before age 18 years, though no difference between sexes was seen after age 18 years. Further support could be seen in that females had a higher proportion of severe asthma than males in young adulthood. These aspects need to be considered by healthcare workers who diagnose and treat individuals with asthma.

In a healthcare setting, it is important that adequate diagnostic tools are being used to identify asthma patients. However, a previous Swedish cross-sectional study of children in primary healthcare centers showed that only 22% of children aged 6 years and older with an asthma diagnosis had ever undergone a spirometry test (142). In **Study III**, the number of registered spirometry tests was also very low, with one or more spirometry registered among only 16% of the participants with persistent asthma during the 4-year period after age 18 years. A previous study showed that not having had lung function testing at the time of initial diagnosis of asthma was associated with failure to have current asthma confirmed (143). The asthma diagnosis should be confirmed, to avoid unnecessary or overtreatment or missing other diagnoses (1). Moreover, a single low measure of lung function measured with spirometry may not represent a true estimate of an individual's later risk of obstructive disease (34). On the other hand, repeated low measurements may indicate persistent reduction or rapid decline in lung function over time, which are more likely to be associated with an

increased risk of chronic obstructive pulmonary disease in early adulthood. It is therefore important that adolescents and young adults with asthma have regular follow-up visits, even if their asthma is mild (144). **Study III** showed that registered healthcare consultations were fewer than recommended in international and Swedish guidelines.

5.1.2 Asthma phenotypes and trajectories

In **Studies I, III, and IV**, several asthma phenotypes and trajectories were identified and characterized. Through identification and characterization of asthma phenotypes and trajectories, asthma management can be individualized and made multidisciplinary, to ensure the best outcomes (145). In **Study IV**, a hypothesis-free approach was used. The results were in line with those of other studies, which have identified similar classes to describe childhood asthma trajectories (40). The unbiased studies have often identified 3 to 5 trajectory groups. The variations in the number of identified trajectories may be explained by differences in study populations, sample size, asthma definitions, or frequency and timing of data collection (42).

When the trajectories in **Study IV** were characterized, established background factors were seen to be associated with the trajectories of age at onset of asthma. For example, family history of allergic disease was associated with a persistent wheeze trajectory in childhood (2). Moreover, higher proportions of parental smoking at baseline seemed to characterize the early-onset transient asthma trajectory (40). Factors such as "being breastfed," "having an older sibling," and "having a furred pet" at baseline also characterized the early-onset transient asthma trajectory. Results from a previous Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study showed that having older siblings in the first year of life increased the risk of transient early wheeze (146). On the other hand, a previous study observed a reduced risk of intermediate-onset wheeze (appearing at around 18 months) for those who had a dog in the household at baseline and for first-born children (147). However, a previous study found little evidence of the association between wheeze trajectories and pet ownership (148). Moreover, results from a previous study pooling 11 European birth cohorts together found that pet ownership in the first 2 years of life did not increase or reduce the risk of asthma in children aged 6–10 years (14). Further, most participants with early allergic co-morbidity belonged to the adolescent-onset and persistent asthma trajectory groups. In the same trajectory groups, about one third had eczema and were sensitized to food allergens at early ages. Positive IgE sensitization to inhalant allergens increased with age in all trajectories, following the concept of the atopic march (16, 17, 149). Sensitization to allergens

is thought to have an important role in the development of asthma (15). Despite some overlap with other asthma trajectories, allergic asthma may be classified as its own distinct trajectory.

In the separate comparison between the adolescent-onset and persistent asthma trajectory groups in **Study IV**, the results showed that these groups seemed to have equal burdens of respiratory markers, such as severity of disease and impaired asthma control, in adolescence and young adulthood, even though the adolescent-onset trajectory group had a more recent onset of disease. However, the persistent asthma trajectory group, with the highest proportions of high FeNO and high eosinophil counts, had more signs of type-2 inflammation (150) than the adolescent-onset trajectory group. Further, the persistent asthma trajectory group had lower mean values of FEV_1 and FEV_1/FVC, and a higher proportion of airflow limitation in adolescence. These results were in line with a previous study showing that asthma patients with increased FeNO and eosinophil counts had a higher prevalence of impaired lung function and uncontrolled asthma compared with patients with normal levels of these inflammatory markers (128).

5.1.3 Management of adolescents and young adults with asthma in relation to guidelines

The long-term goal of asthma management is to achieve control of symptoms through, e.g., treatment (1, 8, 64). ICS can control asthma by optimizing lung function and reducing symptoms and disease burden (1, 58). Despite this, almost half of the adolescents with asthma in **Study I** and about two thirds of the young adults with persistent asthma in **Study III** had an uncontrolled disease. Adherence to ICS is poor, leaving patients exposed to the risks of SABA-only treatment (151, 152). In the new GINA guideline recommendations, treatment of asthma with SABA alone is no longer suggested for adults and adolescents (56). This underlines the importance of increased understanding of asthma and asthma management (153).

Basic asthma management requires self-management education, optimization of inhaler technique and treatment adherence, and avoidance of environmental triggers (1, 82). Adolescents and young adults with asthma are often treated in primary care, and ideally in a team with a registered nurse (154). Primary care nurses can make significant contributions to improve health outcomes for patients with a chronic disease (155). Written action plans for managing worsening symptoms and structured education provided by asthma nurses are prioritized actions in the Swedish National Board of Health and Welfare's guidelines (50). Self-management is an important factor in asthma control, and results from a recent Swedish study showed that knowledge of self-management procedures among adults with asthma was

associated with a written action plan, advanced treatment, higher educational level, physician continuity, and, in females, visiting an asthma nurse (156). In contrast, the participants in **Study II** expressed a feeling of impersonal contact and experienced a lack of engagement in adult healthcare. This was also found in a recent systematic review of qualitative studies exploring people's experiences of living with severe asthma (157). People with severe asthma try to achieve a greater level of personal control over their condition, but they receive lacking support from their healthcare providers. This highlights the importance of bridging the gap in asthma management among adolescents and young adults (**Figure 13**).

Adherence to ICS is an important part of asthma management throughout life, and may be especially challenging during the transition into adulthood (58). Low numbers of dispensed asthma medications were seen for all asthma phenotypes in **Study III**. Moreover, during the study period of eight years, almost no one was dispensed asthma medications regularly. The overall rate of optimal adherence to asthma medications is generally low (between 22 and 63%), and adolescents with asthma typically report poorer adherence than children and adults (58, 59). A recent systematic review found that the prevalence of adherence to ICS was 28% in young adults (mean age between 15 and 30 years) (58). This may be due to the increase in self-management in medication and other self-care responsibilities that occurs during adolescence. Previous studies have also shown that children's dispensing patterns of asthma medications are affected by siblings, as they may share asthma medications (108, 158). Socioeconomic status also impacts on dispensation; when assessing the effect of an eliminated patient fee on asthma medications, the volume dispensed per child increased for families with a low socioeconomic status. Moreover, a recent systematic review found two factors significantly associated with adherence among adult patients with severe/"difficult-to-treat" asthma: male sex and a better asthma-related quality of life score (159). Further, sex is known to affect the dispensing patterns of asthma medications in children, including adherence to controller medication (higher among boys) (160). A difference in dispensing patterns in relation to sex was also seen in **Study I**. Males had been dispensed high daily doses of ICS or fixed combinations of ICS and LABA more than females (this also correlated with the higher mean number of consultations before age 18 years among males in **Study III**). The additional data from the 24-year follow-up showed the same results, although the difference was not statistically significant, indicated that females are undertreated and underdiagnosed (23).

Furthermore, using the definition of severe asthma in this thesis, partly based on the requirement to fulfil criteria for asthma and dispensations of high daily doses of ICS, a smaller group among the participants with asthma was found to have severe asthma.

However, the prevalence was in line with a previous Swedish population-based study (70). The definition of severe asthma is not unambiguous, and establishment of an improved definition – including risk assessment and a reflection of the clinical reality – has been suggested (161). Moreover, the prevalence and the characteristics of patients with "severe asthma" most likely differ depending on region, climate, healthcare system, and reporting (161). Prior to 2000, there were no consensus definition of "severe asthma" (162). In 2014, a joint task force, supported by the ERS/ATS, provided recommendations and guidelines in children and adults on the evaluation and treatment of severe asthma (73). In 2018, the ERS Severe Heterogeneous Asthma Research collaboration, Patient-centered (SHARP) Clinical Research Collaboration (CRC) was set up to harmonize severe asthma management across Europe and deal with the underlying heterogeneity (163). In a recent study from the SHARP CRC, the group highlighted a need for agreement between ERS/ATS and GINA guidelines, as the differences in definitions could be confusing for physicians (161). Ideally, an international consensus should be reached on a set of key variables that can be collected in national registries to increase their usability.

Figure 13. An illustration of bridging the gap in asthma management among adolescents and young adults.
Illustrated for this thesis by FB Scientific Art Design 2021.

5.1.3.1 The transition from pediatric to adult healthcare

A chronic disease like asthma may cause deterioration among patients in adolescence, prior to or following the transition to adult healthcare (164). In **Study III**, uncontrolled asthma among the participants with persistent asthma (asthma at both the 16- and 24-year follow-ups) increased significantly following the transition to adult healthcare. In **Study IV**, about half of the patients in the adolescent-onset and persistent asthma trajectory groups had a uncontrolled disease at 24 years of age. More than a tenth in the persistent asthma trajectory group had airflow limitation and more than a third had a high eosinophil count at 24 years of age.

However, there is guidance for clinicians on the transition from pediatric to adult healthcare (88). To support the transitional care of adolescents and young adults with asthma, the European Academy of Allergy and Clinical Immunology (EAACI) recently developed a clinical practice guideline to provide evidence-based recommendations for healthcare providers (86). Further research is needed to assess whether transition guidelines are used and have a long-term impact on care (90). Healthcare providers' adherence to transition guidelines appeared to be inadequate, based on the results in **Studies II** and **III**. In **Study II**, some of the young adults did not know a transition should occur when they were around 18 years of age. System barriers, such as not receiving information on the transition, have been identified in earlier studies, emphasizing the need for better communication between pediatric and adult healthcare during the transition process (165, 166). In **Study III**, registered healthcare consultations were fewer than recommended in international and Swedish guidelines for all asthma phenotypes (1, 49, 50), and their frequency decreased after the transition. Regarding level of care, the mean number of healthcare consultations to specialist care was found to decrease after age 18 years, while the number of visits to primary care increased. Given that Swedish primary care is responsible for providing basic medical treatment, the result was as expected (167). However, most of the participants attending specialist care before age 18 years had no healthcare consultation either in primary or specialist care after age 18 years. To ensure continuity, patients who are managed well in primary care can remain there, but the majority of adolescents with asthma requiring a tertiary level of care would be expected to need specialist care as adults (144). A recent U.S. study investigated clinician-reported adherence to asthma guideline recommendations, and found that agreement with and adherence to guidelines was higher among specialty physicians than among primary care physicians. It also found overall low adherence with, e.g., use of written action plans and medical procedures (52). Based on the literature and

results from this thesis, it can be concluded that there is a gap between asthma guidelines and actual management (88, 93, 96, 98, 123, 165, 168, 169).

Teamwork between the pediatric and adult systems is key to improving communication and coordination in the transition from pediatric to adult healthcare (88). Team-based care in both the pediatric and adult settings could increase the chances of success. The basics of transition, common to all diseases and conditions, are to prepare young adults in advance for moving to adult healthcare, to prepare adult services to receive the young adults, and to listen to the young adults' own ideas of what they want from the transition (88, 170). The focus is often on children, and healthcare relies on parents reporting asthma symptoms, but responses in adolescence and young adulthood are not the same, with adolescents and young adults expected to be independent patients and to self-manage their asthma (83). A recent doctoral thesis investigating patient empowerment during the transition to adulthood in young persons with chronic conditions discussed the importance for young people to be empowered and to feel capable of asking questions and participating in the healthcare process (87). Developing their communication skills will facilitate their participation in adult healthcare once they are transferred. Further, the results showed that in young persons with a congenital heart disease, patient empowerment was correlated with transition readiness. Moreover, a previous published qualitative meta-synthesis of adolescents' and young adults' experiences of the transition from pediatric to adult hospital care showed that this was more than a change from one place to another (123). It is known that these experiences are linked into a pattern of developmental, health-illness, organizational, and situational transition issues. The authors also identified feelings of not belonging, similar to those among the young adults in **Study II**, and the needs among young adults to be acknowledged as competent during the transition process, across chronic diagnoses.

5.2 Methodological considerations

5.2.1 Random errors

Epidemiological studies may be afflicted by two types of error: random or systematic errors (**5.2.2**) (171). Random errors originate from the sampling variability. Sample size is a source of random errors, and to reduce sampling errors one way is to enlarge the size of the study (172). The CI indicates the amount of statistical variability: a wide CI implies low precision and a narrow CI implies high precision (171). Due to the limited number of subjects with, e.g., high blood eosinophil cell count and severe asthma, it could be difficult to draw conclusions like those drawn in **Study I**, where a wide CI was seen for high blood eosinophil cell count when investigating "sex and clinical characteristics in relation to uncontrolled

asthma among adolescents with asthma at age 16 years." In **Study III,** when investigating "asthma phenotypes at the 16-year follow-up in relation to one consultation after age 18 years among young adults with persistent asthma," the wide CI of severe asthma indicated a statistical uncertainty. However, this was a population-based study; participants with high blood eosinophil cell count and severe asthma were expected to be fewer than in selected patient populations.

5.2.2 Systematic errors

In contrast to random errors, systematic errors do not depend on the study size or chance. A study can be biased because of how the participants have been selected (selection bias) or how the variables have been measured (information bias), or because of some confounding factor that is not completely controlled (171). Selection bias, information bias, and confounding are the most common systematic errors.

5.2.2.1 Selection bias

In this thesis, selection bias might have occurred from the procedures used to select participants during the recruitment of the BAMSE cohort, the study populations, and when participants were loss to follow-up (171).

During the recruitment of the BAMSE cohort, 477 families could never be reached and 1,256 were actively excluded due to that the family planned to move within 1 year of the project start, had insufficient knowledge of Swedish, had a seriously ill child, or an older sibling was already included in the study (**Figure 4**) (105). The short questionnaire to evaluate the representativeness of the included children in the BAMSE cohort and the excluded and non-responding families showed that there were no major differences regarding family history of allergic disease and other known risk factors for allergic disease – except for parental smoking, which was more prevalent among the excluded and non-responding families than among the included families. Since comparisons in this thesis have been made within the cohort, non-participation in the baseline questionnaire has most likely not introduced bias in the observed associations between the exposure and outcome.

Selection bias may occur in longitudinal studies due to loss to follow-up. The BAMSE cohort has a low rate of loss to follow-up (at age 16 years, 76% of the participants completed the questionnaire, and at age 24 years, 75%), comparable to the 72% response rate at age 20 years in the German Multicentre Allergy Study (MAS) birth cohort study (173). A low rate of loss to follow-up reduces the risk of selection bias.

To evaluate possible selection bias, **Studies I** and **III** included comparisons of the characteristics of the study populations and those of the original BAMSE cohort, showing minor differences. The statistically significant differences for parental allergic disease, higher parental education, and female sex most likely did not affect the observed associations. Still, selection bias cannot be ruled out. For example, participants with a history of allergic disease have remained in the BAMSE cohort more often than those without a history of allergic disease, which might lead to an overestimation of asthma prevalence.

5.2.2.2 Information bias

Information bias can occur if the collected information about or from the study participants is incorrect (171). Such information is often referred to as misclassification. Misclassification can be non-differential or differential. Non-differential misclassification is distributed equally in relation to the exposure or outcome, leading to a dilution of the association (171). Differential misclassification is not equally distributed in relation to the exposure and outcome, which can cause an over- or underestimation of the association.

There are reports of under- and over-diagnosis of asthma in children (138, 174). In this thesis, definitions of asthma were based on questionnaire reports of validated and widely used questions (33, 106). A recent study investigating the agreement of parental responses to asthma-related questions regarding their children and Swedish healthcare registers found good agreement (175). This indicates that questionnaires are appropriate proxies for asthma in general and can be used for healthcare research. However, in this thesis, the definitions of asthma were based on parent-reported data up to 8 years of age, and on the participants' answers from age 12 years. In the BAMSE project, a previous study based on the 12-year follow-up examined whether there was a difference between children and parents in reporting symptoms and treatment of allergic diseases and found that the children reported more symptoms than their parents, whereas questions about pharmacological treatment had high levels of agreement (176). However, some misclassification is difficult to avoid, as people may interpret questions differently or may not remember accurately.

In the LCA in **Study IV**, longitudinal data were used, with the same definition of asthma from infancy up to young adulthood. At infancy (at 1 and 2 years of age), this definition of asthma (i.e., fulfilling at least two of the following three criteria: symptoms of wheeze and/or breathing difficulties in the preceding 12 months, ever doctor's diagnosis of asthma and/or asthma medication occasionally or regularly in the preceding 12 months) was somewhat more stringent than the definition of, e.g., the Swedish Pediatric Society (49). Accordingly, asthma in children (non-IgE-mediated or in combination with eczema, food

allergy or family history of allergic disease) before the age of three years, was diagnosed after three episodes of wheeze. After three years of age, an asthma diagnosis could be made after one episode, or before that if the child had IgE-mediated asthma or in combination with eczema, food allergy or family history of allergic disease, and/or repeated episodes in between. The non-differential misclassification may have caused an underestimation of asthma at 1 and 2 years of age in **Study IV**. There is no gold standard in defining asthma during childhood, and there is a trade-off in between using a strict definition, and missing cases (high specificity – the proportion of participants without the disease, who have a negative result of the test/symptom – but low sensitivity – the proportion of participants with the disease who also have a positive result of the test/symptom (171)) and using an inclusive definition and classifying cases as non-cases (high sensitivity, but low specificity).

Other potential sources of misclassification are the modified GINA definition of asthma control, which was based on information for the 12 months preceding each questionnaire; the GINA guidelines base asthma control on information from the last 4 weeks (1). The non-differential misclassification may have led to an overestimation of the proportion of adolescents and young adults with uncontrolled asthma in the studies included in this thesis. Moreover, an overestimation of the prevalence of severe asthma in **Studies I, III,** and **IV** may be present, due to the participants not undergoing a systematic assessment to differentiate "severe asthma" from "difficult-to-treat" patients, in whom poor control is related to factors such as poor adherence or co-morbidities (35). Also, the cut-off values of the treatment with "high" daily dose of ICS or fixed combinations of ICS and LABA differ between studies. In this thesis, GINA's suggested "high" dose was used (1). The misclassified participants would be equally distributed in relation to the exposure and outcome, which would imply a non-differential misclassification.

The risk of misclassification is lower for objectively collected data. The examinations of blood sampling, lung function, and height and weight were standardized and performed by trained nurses. However, different cut-off values were used for blood eosinophils: > 0.5 (10^9 cells/L) in **Study I** and > 0.3 (10^9 cells/L) in **Study IV**. Both are widely used in literature (35, 129). For neutrophils, different cut-off values were also used. However, in a recent study, it has been discussed that the level of blood neutrophils does not accurately predict airway neutrophils and that neutrophilic airway inflammation can only be assessed by induced sputum (35). In this population-based cohort, sputum analyses of neutrophils have not been performed. Further, it has been suggested that a FeNO > 50 ppb indicates eosinophilic airway inflammation and responsiveness to corticosteroids (in this thesis defined as ≥ 25 ppb), and

that a value of 25–50 ppb should be interpreted carefully with reference to the clinical context (177).

Information gathered via healthcare registers has many strengths, but may theoretically have limitations. When using the national VAL register in **Study III**, a sensitivity analysis with wider ICD-10 codes was performed to assess potential underreporting or misclassification of diagnoses. This showed comparable results, indicating a small potential of non-differential misclassification in asthma diagnoses. Moreover, as patients have the right to seek healthcare anywhere in Sweden, irrespective of which region they live in, a non-differential misclassification of the number of healthcare consultations in **Study III** may be present, as it is common for young adults to move from their hometown due to studies in another city. To minimize the risk of non-differential misclassification, the study population was restricted to include only participants who lived in the Stockholm region at both the 16- and the 24-year follow-ups.

Moreover, a previous study validated asthma diagnoses in the regional SPDR and suggested that asthma medication in the SPDR could be used as proxy for asthma (178). In gathering information on dispensed asthma medicines via the SPDR, my coresearchers and I used an 18-month window, based on information from a previous study comparing the concordance between register data and dispensed medicines and parental/self-reported use of asthma medicines in adolescents (179). The study found that the best general agreement with the questionnaires was the 18-month time window (the different time windows were: 3, 6, 12, 18, and 24 months prior to the respective questionnaires). The highest concordance between the register and reported use was seen for adolescents with severe asthma. Moreover, when investigating dispensed asthma medicines in registers, it is important to consider irregularities in purchasing asthma medicines due to the variability in the disease over time.

5.2.2.3 Confounding

In general, a confounder must be associated with both the exposure and the outcome, and it occurs when the association between the exposure and outcome is attributable to another exposure (a third factor) (172). Confounding indicates that the effect of the exposure is mixed with the effect of another variable, meaning that the association is due to another factor than the investigated exposure, leading to a bias (171). The confounding factor can cause a decreased or an increased association. There are three methods to prevent confounding: randomization, restriction, and matching (171). To control for confounding in the analysis, two methods can be used: stratification and regression models (171). However, the influence of unmeasured and unknown confounders cannot be ruled out in any non-randomized trials.

The BAMSE study's prospective design and extensive information on background and allergy-related symptoms allowed evaluation of potentially confounding factors. In **Studies I** and **III**, a hypothesis was that sex could be a confounding factor when investigating adolescents and young adults with asthma in relation to uncontrolled disease, adolescent-onset asthma, and healthcare consultations. To control for sex, analyses were therefore stratified and adjusted for sex (among other things). Additional data in this thesis – asthma control, asthma with high daily doses of ICS, and severe asthma at age 24 years – were also stratified for sex. Logistic regression models were used in **Studies I** and **III** and tested for confounding. Factors were included in the adjusted model based on *a priori* knowledge. Although a number of variables were considered to be potential confounders in this thesis, residual confounding (factors that are not controlled for or factors that are controlled for, but measured inaccurately) may have been present (171).

5.2.3 Generalizability

Generalizability, or external validity, is the degree to which the results of an observation can be applied in other settings (180). This thesis was based on the BAMSE study – with a population-based design and a large and well-characterized study sample. In the final cohort consisting of 75% of the eligible children, parental smoking was more prevalent among the actively excluded and the non-responding families than among the included families. However, history of allergic disease did not influence the motivation to participate, thus it may be assumed that the results in this thesis can be generalized to other similar populations in urban-industrial settings. The prevalence of asthma and the asthma phenotypes corresponded well with those seen in other Swedish (30, 70, 181, 182), Nordic (72, 183), and European studies (184).

The results were based on the Swedish population and the generalizability to other countries may be discussed for **Study III**, since healthcare systems vary between countries; modes of payment, the uses of specialist services, and reimbursement systems also vary (110). However, the transition from pediatric to adult healthcare is an international concern, and the results can most likely be transferred to other countries and populations.

5.2.4 Strengths

The strengths of **Studies I, III** and **IV** (quantitative) in this thesis included the population-based prospective design, the high participation rate, the repeated assessments of allergic diseases, and the combination of clinical objective data such as IgE sensitization, lung function, and height and weight. Another strength was the use of register data through linkage

to mandatory Swedish health registries, with high quality and coverage. The national SPDR provided complete data on the number of individuals exposed to dispensed prescribed medications in the Swedish population (114). The regional VAL database has approximately 85% coverage of all diagnoses in primary care, more than 90% coverage of utilization in specialist care, and more than 99% coverage of hospital care (185).

5.3 Methodological considerations in relation to qualitative research

In **Study II**, the STC approach was used to analyze qualitative data. The procedures of STC are simple and accessible for novices, although with limited room for creative interpretations and elegant conclusions (121). The detailed descriptions of the procedures for analysis with STC support transparency and intersubjectivity, as the procedures are easy to conduct and present. However, a range of methods can be applied in qualitative analysis, and a transparent description of the path from data to results is necessary to convey to the reader what was done (118). In **Study II**, there are various aspects of *trustworthiness*. To show c*onfirmability*, the researchers reflected on their preunderstanding of having different experiences of the specific aim being investigated and the method being used (186, 187). Further, in recruitment, the sex aspect was kept in mind, to uncover potential differences in perceptions since sex differences have been revealed, e.g., girls are less likely to achieve asthma control than boys (115). However, socioeconomic status was not taken in account, which could be associated with certain experiences of the transition process. Through the purposive sampling, *credibility* may have been achieved thanks to the varied selection of participants which provided multiple perspective of the phenomena in relation to the specific aim (125). The sample also promoted *credibility* as the participants gave sufficient variety to highlight the purpose (117, 187). The sample size was based on "information power" and factors having an impact were the quality of dialogue, the relevant and purposive sample, the narrow aim, and the chosen analysis strategy (120).

Individual interviews were performed, but a group context could have been used instead. The advantage with focus groups, for example, is the interaction in a group context which can result in a broader perspective, as participants are more likely to express their opinions after listening to others in a similar situation (117, 186). Moreover, the interviews with open-ended questions were based on an interview guide. Using an interview guide strengthens the *dependability* of a study. Other advantages are that it helps the researcher to focus on different perspective of the phenomenon that they are investigating and that all the participants are given the same questions (125, 186). In this case, it also saved time due to the dross rate being lower than in unstructured interviews (186). When the interviews were

performed, the participants had a mean age of 23.4 years (range 22.4–24.5). This means that the participants were likely to remember what it was like 4–6 years earlier, when they should have transferred from pediatric to adult healthcare. This could be a disadvantage, which might have been solved by using another way of recruiting the participants, e.g., adolescents who were in the midst of the transition, i.e., 18 years of age at the time of the interviews. However, in general, participants tell their story from their perspective, even if their memories are selective. The accuracy of the interview data is not as important as the motivations and thoughts of the participants (186). Through descriptions of when in time the data were collected, the reader gets a clue to the stability as well as the *dependability* in the collected material over time.

To achieve *credibility* in the analytical process, all steps were first conducted by the author of this thesis and then separately by the co-authors of the respective studies. The authors discussed their results jointly, until they reached agreement (125). Researchers triangulate to corroborating evidence to validate the accuracy of a study (124). *Credibility* also deals with how to assess similarities within and differences between categories (125). A way of approaching this is to show representative quotations from the transcribed text.

Results of qualitative studies cannot be *generalized*, but can be *transferred* to other settings and groups (188). However, **Study II** can be argued to add new knowledge through the participants' various experiences of the transition process, which can promote reflection among healthcare providers on how to manage the transition from pediatric to adult healthcare.

A non-theory-driven inductive procedure was used in the analysis of the material in **Study II**. Thus, no theoretical framework was used; in STC, the role of theoretical frames of reference for analysis can be applied in different ways. A range of theories can be applied to support STC analysis, depending on the specific research question of a study (121). Theories can be used to frame a research question, guide the selection and interpretation of data, and as a basis for explanations of the causes underlying observed phenomena (189). However, the purpose and impact of theoretical perspectives are regularly debated in qualitative research. There is considerable variation regarding theoretical commitment; some prefer studies without a hint of theory, others prefer those where empirical findings disappear among comprehensive undigested theoretical elaborations (189).

6 Conclusions

Based on the results from this thesis, it could be concluded that asthma was common in adolescence and young adulthood, and a shift from male to female dominance occurred during adolescence. Further, many adolescents and young adults had few asthma-related healthcare consultations and dispensed asthma medications. Moreover, the adolescents and young adults with more recent onset of disease had equal burdens of respiratory markers as those who had persistent symptoms.

The following specific conclusions could be drawn from **Studies I-IV**:

- About half of the adolescents with asthma had an uncontrolled disease, which was more common among females. Morover, females more often had adolescent-onset asthma than males. Although this is quite uncommon, some of the adolescents with asthma have severe asthma.

- Asthma-related healthcare consumption and pharmacological dispensations were fewer than recommended and decreased after the transition from pediatric to adult healthcare. Further, based on the young adults experiences' of the transition, participants felt that they did not know where to turn within adult healthcare, and they wanted healthcare providers to involve them in self-management already during adolescence.

- Using a hypothesis-free approach, four asthma trajectory groups were identified from infancy to young adulthood, as were their associations with lung function and inflammatory and respiratory markers in adolescence and young adulthood. The adolescent-onset and persistent asthma trajectory groups had equal burdens of asthma control and severity in adolescence and young adulthood. However, the persistent asthma trajectory group showed more signs of type-2 inflammation than the adolescent-onset trajectory group.

6.1 Clinical implications

Studies I-IV have the following clinical implications:

- The results highlighted the clinical relevance of monitoring the treatment of asthma in adolescents and young adults, especially among patients with uncontrolled and severe asthma, and in females.

- The results highlighted that healthcare providers should increase their understanding of the difficulties that young adults with asthma face during the transition from pediatric to adult healthcare. It is suggested that healthcare providers work together with each patient to prepare, plan, and communicate in the progressive transition process, to acheive continued care in line with current guidelines.

- The results showed that there was a need for healthcare providers to be aware of and identify patients in adolescent-onset and persistent asthma trajectory groups, in order to optimize management. These are vulnerable groups that suffer similar levels of deficits in asthma control.

7 Points of perspectives

As a continuation of my research for this thesis, and the overarching aim to make significant contributions to the knowledge base regarding how the management of adolescents and young adults with asthma can be improved, I would like to further explore and advocate future research.

- **Asthma management – hospital-based material**

This thesis is population-based, however it would also be interesting to investigate e.g., the prevalence of severe asthma including a systematic assessment and differentiate "severe asthma" from "difficult-to-treat" in patients treated at specialized allergy clinics.

- **Parents perspective of the transition process – a qualitative study**

This thesis produced less knowledge about the parents perspective of the transition from pediatric to adult healthcare, therefore to gain further knowledge regarding their experiences of the management during the transition process it would be of great intrerest to e.g. perform focus group interviews.

- **Impact of the disease in young adulthood – a cross-sectional study**

In the BAMSE cohort, health-related quality of life (HRQoL) has previously been investigated using the generic instrument EQ-5D (190). At age 8 and 16 years, children with asthma had a lower median EQ visual analogue scale value than children without asthma (191, 192). In adolescence, the impairment was most pronounced if asthma was uncontrolled (192). Previous studies has shown that adolescent males with asthma report better HRQoL than female peers (26, 193-195). It would be interesting to compare HRQoL in young adults with asthma, as they now have become independent adult patients. Also, the influence of the transition process on stress and mental illness among young adults with asthma.

8 Popular science summary of the thesis

Asthma is one of the most common chronic diseases during childhood. The goal of asthma treatment is to achieve and maintain asthma control and to reduce future risks of exacerbations. With asthma medication and support for self-care, this should be possible to achieve for the vast majority of patients. However, this is not always the case, particularly among adolescents and young adults. Adolescents and young adults thus have an increased risk of uncontrolled asthma compared with younger children. Children with more severe asthma are typically treated in children's hospitals, but a transfer to adult healthcare is carried out when they are around 18 years old. One hypothesis is that the young person loses contact with healthcare during this period. The overall aim of this thesis was to characterize asthma in adolescence and young adulthood with a particular focus on sex and severity, and to identify factors of importance for improved asthma management during the transition from pediatric to adult healthcare.

All four studies in this thesis were based on the ongoing Swedish BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology) study. The BAMSE study included 4,089 participants born between 1994–1996. The participants have been followed since infancy with regular follow-ups, including questionnaires and clinical examinations; the latest follow-up was when the participants reached age 22–24 years.

Study I investigated how many of the participants who had asthma during adolescence, in relation to sex and severity of disease. Overall, it was found that asthma in adolescence was common (14%), and a small group of adolescents had severe asthma, although this was quite rare. Females had asthma more often than males. About half of the adolescents with asthma had an uncontrolled disease. This was more common among females.

Study II examined young adults with severe asthma and their experiences of the transition from pediatric to adult healthcare. Individual interviews provided a deeper insight and revealed weaknesses in the transfer process, as the young adults felt that they did not know where to turn and experienced fewer follow-ups in adult healthcare. Further, the young adults wanted the caregivers to involve them in self-care during adolescence. In general, they felt that their asthma received insufficient attention from the caregivers.

Study III investigated the care of adolescents and young adults during the transition from pediatric to adult healthcare. To do this, information was gathered from Swedish registers of asthma-related dispensed medicines and healthcare contacts. The results showed that the healthcare contacts were fewer than recommended and decreased after the transfer to adult healthcare. In addition, almost no one had regular asthma treatment during the transfer process.

Study IV identified different types of asthma from infancy to young adulthood and patient groups were characterized based on, among other things, asthma control and severity of disease. Those who had a late debut and those who had persistent asthma were found to have a similar burden of asthma control and severity during adolescence and young adulthood.

In summary, the results suggested that asthma was common among adolescents and young adults. About half had uncontrolled asthma during adolescence; this was more common in females than males. Through identification and characterization of different types of asthma, management and treatment can be individualized. Due to the shortcomings in the transition from pediatric to adult healthcare, where management is not carried out in accordance with guidelines for asthma, it is an important task for healthcare to identify the young people who need more healthcare and closer follow-ups to prevent disease deterioration.

9 Svensk populärvetenskaplig sammanfattning

Astma är en av de vanligaste kroniska sjukdomarna under barndomen. Målet med astmabehandling är normal lungfunktion och att kunna leva ett gott liv utan begränsningar i dagliga aktiviteter, med så få symtom som möjligt. Med astmamediciner och stöd till egenvård bör det kunna uppnås för det stora flertalet. Dock är så inte alltid fallet och speciellt stort är problemet bland ungdomar och unga vuxna. Ungdomar och unga vuxna har därmed en ökad risk för okontrollerad astma jämfört med yngre barn. Barn med svårare astma behandlas och följs vanligen på barnsjukhusen, men när ungdomarna är kring 18 år ska en överföring till vuxensjukvården genomföras. En hypotes är att den unga personen tappar kontakten med sjukvården under den här perioden. Det övergripande syftet med den här avhandlingen var att undersöka astma hos ungdomar och unga vuxna med ett särskilt fokus på kön och astmans svårighetsgrad samt att urskilja viktiga faktorer för förbättrat omhändertagande under överföring mellan barn- och vuxensjukvård.

Samtliga fyra delstudier i den här avhandlingen baserades på den pågående svenska BAMSE (Barn, Allergi, Miljö, Stockholm, Epidemiologi)-studien. BAMSE-studien inkluderade 4,089 barn födda mellan 1994 och 1996. Deltagarna har följts sedan spädbarnsåren med regelbundna uppföljningar i form av frågeformulär och kliniska undersökningar och den senaste uppföljningen var när deltagarna nått 22–24 års ålder.

I **delstudie I** undersöktes hur många som hade astma i tonåren i relation till kön samt astmans svårighetsgrad. Resultaten visade att astma i tonåren var vanligt (14%), men att få ungdomar hade en svår astma. Kvinnor hade oftare astma än män. Ungefär hälften av ungdomarna med astma har en okontrollerad sjukdom, vilket var vanligare bland kvinnorna.

I **delstudie II** undersöktes unga vuxna med svårare astma och deras erfarenheter av överföringen från barn- till vuxensjukvård. Individuella intervjuer gav en djupare inblick och avslöjade brister i överföringsprocessen, då de unga vuxna upplevde att de inte visste vart de skulle vända sig och upplevde färre uppföljningar inom vuxensjukvården. Vidare ville de unga vuxna att vårdgivarna skulle involvera dem i egenvården under tonåren samt ansåg att deras astma fick otillräckligt stöd från vårdgivarna.

I **delstudie III** undersöktes omhändertagandet av ungdomar och unga vuxna under överföring från barn- till vuxensjukvården. För att göra detta användes även information från svenska register över astmarelaterade köp av mediciner samt sjukvårdskontakt. Resultaten visade att sjukvårdskontakterna var färre än vad som rekommenderas och dessutom minskade efter överföringen till vuxensjukvården. Få ungdomar med astma hade regelbunden astmabehandling under överföringsprocessen.

I **delstudie IV** identifierades olika typer av astma från barndom till ung vuxen ålder och dessa typerna karakteriserades utifrån bland annat astmakontroll och svårighetsgrad. Resultaten visade att de som debuterar sent och de som har ihållande astma har liknande nivåer av astmakontroll och svårighetsgrad under tonåren och ung vuxen ålder.

Sammanfattningsvis tydde resultaten på att astma var vanligt bland ungdomar och unga vuxna. Ungefär hälften hade en okontrollerad astma under tonåren, vilket var vanligare bland kvinnor än män. Genom att identifiera och karakterisera olika typer av astma kan omhändertagandet och behandlingen av astma individualiseras. Omhändertagandet av unga med astma sker inte enligt riktlinjerna för astma; därför är det en viktig uppgift för sjukvården att identifiera de ungdomar som behöver fortsatt sjukvård i överföringsprocessen för att förhindra att sjukdomen försämras.

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